UNIVERSIDAD COMPLUTENSE DE MADRID

FACULTAD DE FARMACIA

DEPARTAMENTO DE QUÍMICA ORGÁNICA Y FARMACEÚTICA

UNA VARIANTE DE LA REACCIÓN DE PICTET-SPENGLER Y SU APLICACIÓN A LA SÍNTESIS DE ANÁLOGOS DE ALCALOIDES TETRAHIDROISOQUINOLÍNICOS DE ORIGEN MARINO

TESIS DOCTORAL DE:

FRANCISCO JOSÉ ARROYO SIERRA

DIRIGIDA POR:

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PILAR LÓPEZ-ALVARADO GUTIÉRREZ

Madrid, 2013

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Memoria que para optar al grado de Doctor
presenta

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Directores: José Carlos Menéndez Ramos y Pilar López-Alvarado Gutiérrez
MADRID 2013

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CERTIFICA:

Que el trabajo contenido en la memoria adjunta, titulada:

"UNA VARIANTE DE LA REACCIÓN DE PICTET- SPENGLER Y SU APLICACIÓN A LA SÍNTESIS DE ANÁLOGOS DE ALCALOIDES TETRAHIDROISOQUINILÍNICOS DE ORIGEN MARINO"

que presenta **D. Francisco José Arroyo Sierra** como tesis doctoral, ha sido realizado en los laboratorios de este Departamento bajo la dirección de los Dres. D. José Carlos Menéndez Ramos y Dña. Pilar López-Alvarado Gutiérrez, Profesores Titulares de Química Orgánica.

Y para que conste proceda, expido y firmo el presente certificado en Madrid, a 14 de mayo de 2013

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En Madrid, a 14 de mayo de 2013

Fdo. José Carlos Menéndez Fdo. Pilar López-Alvarado

ABREVIATURAS Y ACRÓNIMOS

Ac	acetilo
Ac_2O	anhídrido acético
AcOH	ácido acético
anh	anhídrido
ac.	acuoso
Ar	arilo
atm	atmósferas
B	base
Bn	bencilo
Boc	*terc*-butiloxicarbonilo
Boc_2O	pirocarbonato de *terc*-butilo (Boc-anhídrido)
Bt	benzotriazol
Bu	butilo
BuLi	butillitio
Bz	benzoílo
°C	grado centígrado
cap.	capítulo
cat	catalítico
Cbz	benciloxicarbonilo
$CDCl_3$	cloroformo deuterado
col.	colaboradores
δ	desplazamiento químico
d	doblete
dd	doble doblete
dec	descompone
DCM	diclorometano
DEAD	azodicarboxilato de dietilo
DEPT	Distorsionless Enhancement by Polarization Transfer
DIBAL-H	hidruro de diisobutialuminio
DIPEA	diisopropiletilamina
DKP	dicetopiperazina
DMAP	*N*,*N*-dimetilaminopiridina
DME	1,2-dimetoxietano
DMF	dimetilformamida
DMSO	dimetilsulfóxido
DMSO-d_6	dimetilsulfóxido deuterado
Ed.	edición
Ed(s)	editor(es)

EM	Espectrometría de masas
eq	equivalente químico
Et	etilo
Et_3N	*N*,*N*,*N*-trietilamina
Et_2O	éter dietílico
EtOAc	acetato de etilo
g	gramo
h	hora
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum correlation
Hz	hertzio
IBX	2-iodoxybenzoic acid
IR	Infrarrojo
^{i}Pr	isopropilo
J	constante de acoplamiento
□	longitud de onda
LDA	diisopropilamiduro de litio
LiHMDS	hexametildisilazida de litio
LNCaP	Lymph Node Carcinoma of the Prostate
M	molar
m	multiplete
Me	metilo
MeOH	metanol
mg	miligramo
min	minuto
mL	mililitro
mmol	milimol
MOM	metoximetil
□	frecuencia
□M	micromolar
NA	no analysis
NBS	*N*-bromosuccinimida
nm	nanómetros
NOE	Efecto Nuclear Overhauser
NOESY	Nuclear Overhauser Effect Spectroscopy
NMO	óxido de *N*-metilmorfolina
N-Troc	*N*-2,2,2-tricloroetiloxicarbonil
Nu	nucleófilo
P.f.	punto de fusión
Ph	fenilo

PIFA	trifluoroacetato de fenilyodonio
ppm	partes por millón
Pr	propilo
Py	piridina
ref.	referencia
RMN	Resonancia Magnética Nuclear
rto.	rendimiento
s	singlete
sa	singlete ancho
SAR	Structure-Activity Relationships
sat	saturada
sept	septuplete
T	temperatura
t.a.	temperatura ambiente
^{t}Bu	*terc*-butilo
TBAF	fluoruro de tetrabutilamonio
TBDPS	*terc*-butildifenilsililo
Tf	triflato
TFA	ácido trifluoroacético
THF	tetrahidrofurano
THIQ	tetrahidroisoquinolina
TMEDA	*N*,*N*'-tetrametiletilenodiamina
TMS	trimetilsililo
TMSCl	cloruro de trimetilsililo
TMSCN	cianuro de trimetilsililo
TPP	trifenilfosfina
TRP	Transient Receptor Potential
TRPM	Transient Receptor Potential Melastatin
TRPM8	Transient Receptor Potential Melastatin member 8
UV	ultravioleta

1. Capítulo 1: Introducción.

1.1. Síntesis de α-amidosulfonas como precursores de derivados de *N*-aciliminio.

1.1.1. Introducción.

La adición nucleófila al doble enlace carbono-nitrógeno es uno de los métodos más convencionales en la obtención de compuestos nitrogenados[1]. Una ineludible comparación con la reactividad del grupo carbonilo, nos muestra una menor electrofilia del agrupamiento azametileno, lo que introduce una serie de limitaciones importantes en la utilización de estos derivados insaturados.

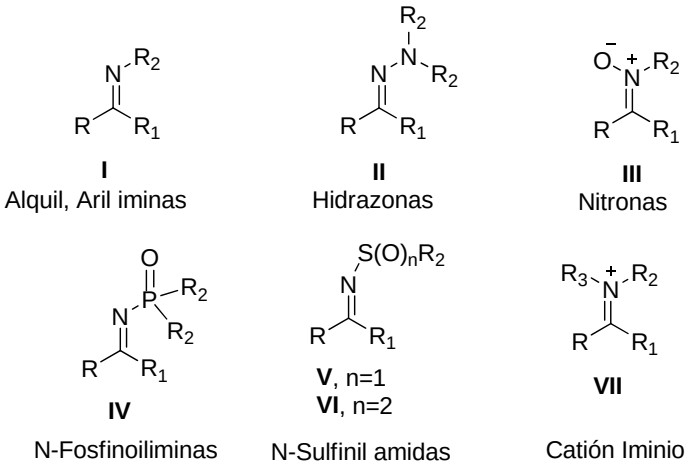
En un intento de mejorar la electrofilia de los enlaces C=N, se ha estudiado la coordinación del par de electrones del nitrógeno con ácidos de Lewis que, aunque en ocasiones aporte un efecto beneficioso, otras veces genera incompatibilidades con el agente nucleófilo presente durante la reacción[2].

Por otra parte, la incorporación de grupos aceptores de electrones en el átomo de nitrógeno, ejerce un marcado aumento en la reactividad en los imino derivados. En este contexto, resulta destacable el empleo de grupos activantes ópticamente activos, que proporcionan un estereocentro durante la adición del agente nucleófilo[3] que puede determinar la estereoquímica del compuesto final. En una clasificación que atiende a la naturaleza del enlace N-X, podemos encontrar:

[1] (a) Volkmann, R. A. en *Comprehensive Organic Synthesis*; Schreiber, S.L., ed.; Pergamon: Oxford, **1991**; Vol. 1, p 355. (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (c) Bloch, R. *Chem. Rev*. **1998**, *98*, 1407. (d) Kobayashi, S.; Ishitani, H. *Chem. Rev*. **1999**, *99*, 1069.

[2] Yamamoto, H., Ed., Lewis Acids in Organic Synthesis; Wiley-VCH: Weinheim, **2000**; vols. 1 y 2.

[3] Alvaro, G.; Savoia, D. *Synlett* **2002**, 651.



Esquema 1. 1

Las *alquil* o *ariliminas* (**I**) al igual que las *hidrazonas* (**II**) son suficientemente estables como para ser sintetizadas y conservadas, pero presentan el inconveniente de no ser particularmente reactivas y de formar enlaces N-R_2 de difícil ruptura una vez producida la adición.

Las *nitronas* (**III**), que pueden considerarse *N*-óxidos de iminas, son más reactivas que las iminas y su reacción con agentes nucleófilos conduce a las correspondientes hidroxilaminas secundarias[4].

Las *N*-fosfinoiliminas (**IV**) han alcanzado una gran relevancia en procesos catalíticos permitiendo la preparación enantioselectiva de aminas primarias[5] (esquema 1.1).

Las *N-sulfinilamidas* (**V** y **VI**) en las que R_2 = ^{t}Bu-, *p*-tolil, no sólo confieren una elevada reactividad al carbono metilénico, sino una alta diastereoselectividad en la adición nucleófila[6]. Las *N*-tosiliminas procedentes de aldehídos aromáticos (R_1 = Ar) suelen ser bastante estables, mientras que las que provienen de aldehídos alifáticos deben prepararse *in situ* y usarse inmediatamente para prevenir su descomposición ó tautomerización a la enamina.

Un considerable incremento en la electrofilia del grupo metileno se consigue generando cationes iminio (**VII**) mediante la *N*-alquilación o bien a través de la eliminación en medio ácido de un grupo saliente adyacente al átomo de nitrógeno. Estos cationes, inestables y

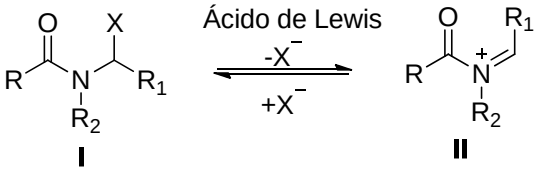
[4](a) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett*, **2000**, 442. (b) Lombardo, M.; Trombini, C. *Synthesis*, **2000**, 759.

[5](a) Spino, C. *Angew. Chem*. Int. Ed. **2004**, *43*, 1764.(b) Kohmura, Y.; Mase, T. *J. Org. Chem*. **2004**, *69*, 6329.

[6](a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Res.* **2002**, *35*, 984. (b) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003.

reactivos, son los agentes electrófilos que participan en la reacción de Mannich, método de síntesis de derivados β-dialquilaminometilcarbonílicos [7].

Por último, los cationes *N*-aciliminio[8] son sustratos muy electrófilos, pero su inestabilidad, que impide su almacenamiento y obliga a su preparación *in situ*, es una seria desventaja frente a otros electrófilos posibles. Los procesos de preparación transcurren principalmente mediante reacciones de eliminación promovidas por agentes básicos o ácidos[9]. Una forma de estabilizar el carbocatión es mediante la presencia de una función carbamato en la estructura (**I**, R = OR', esquema 1.2), facilitando así la disponibilidad del par de electrones del nitrógeno.



I **II**

Esquema 1. 2

1.1.2. Precursores de *N*-acil iminios.

Es evidente que un proceso que genere amidas *N*-sustituidas es necesario a la hora de alcanzar los compuestos de tipo **II** (esquema 1.2). Estos agentes procedentes de la alquilación de amidas comparten la particularidad de poseer un buen grupo saliente (X), por lo cual se pueden clasificar atendiendo a la naturaleza de dicho grupo:

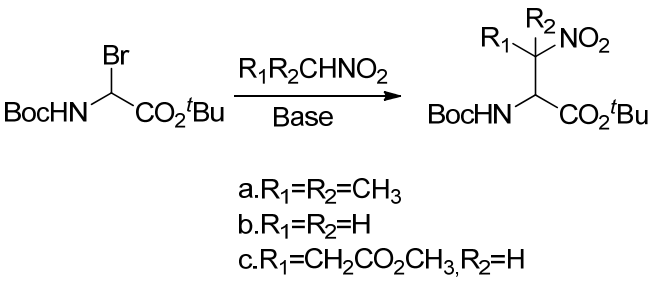
α-Haloamidas (X = Cl, Br), que han encontrado poca utilidad sintética como sustratos electrófilos debido a su inestabilidad. Un ejemplo de su aplicación sintética se resume en el esquema 1.3[10].

[7](a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem.* Int. Ed. Engl. **1998**, *37*, 1044. (b) Bur, S. K.; Martin, S. F. *Tetrahedron*, **2001**, *57*, 3221.

[8](a) Maryanoff, B. E.; Zhang, H. C.;Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem.Rev*. **2004**, *104*, 1431. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron*, **2000**, *56*, 3817. (c) Hiemstra, H.; Speckamp, W. N. Comprehensive Organic Synthesis; Heathcock, C. H., Ed.; Pergamon: Oxford, 1991; Vol. 2, p. 1047.

[9]Zaugg, H. A. *Synthesis* **1984**, 85 y 181.

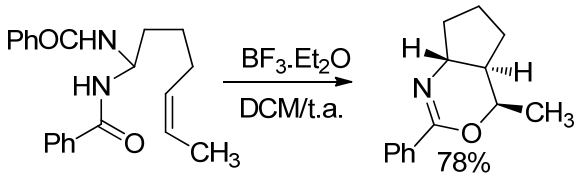
[10]Coghlan, P. A.; Easton, C. J. *Tetrahedron Lett*. **1999**, *40*, 4745.



Esquema 1. 3

α-Oxiamidas y *α-oxicarbamatos* (X = -OR, -OCOR). Son los precursores más explotados para la obtención de *N*-aciliminios, por tratarse de compuestos bastante estables. Pueden ser preparados por oxidación electroquímica de amidas, reducción parcial y otras reacciones a partir de iminas.[11]

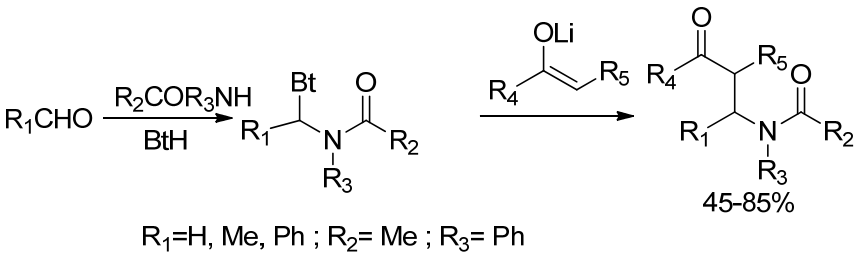
Bisamidas (X = NHCOR, esquema 1.4), que han sido utilizadas principalmente en reacciones de cicloadición[12]



Esquema 1. 4

Derivados de *α-amidoalquilbenzotriazol*[13] (esquema 1.5). Se preparan por reacción entre aldehídos, aminas secundarias y benzotriazol y son eficaces precursores de los agentes electrófilos que nos ocupan.

[11] De Koning, H.; Speckamp, W. N., Stereoselective Synthesis (Houben-Weyl); Helmchen, G., Hoffman, R. W., Mulzer, J., Shaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, **1995**, Vol. 2, p 1047.
[12] Weinreb, S. M.; Scola, P. M.; *Chem . Rev*. **1989**, *89*, 1525.
[13] Katritzky, A. R.; Manju, K.; Singh, S. K.; Meher, N. K. *Tetrahedron* **2005**, *61*, 2555.



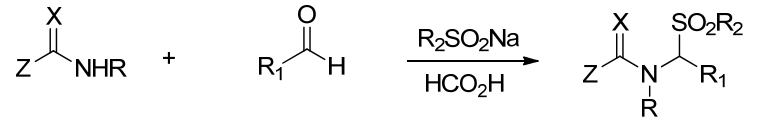
R_1=H, Me, Ph ; R_2= Me ; R_3= Ph

Esquema 1. 5

Las *α-ariltioamidas* (X=SAr) están encuadradas dentro de los grupos salientes pobres, ya que necesitan de fuertes electrófilos para ser eliminadas del correspondiente *N*, *S*-acetal. Por el contrario, las propiedades como buen grupo saliente de la función R-SO_2 de las *α-amidosulfonas* en las reacciones de eliminación están bien documentadas[14].

1.1.3. Antecedentes en la síntesis de α–amidosulfonas.

Engberts y Shating en 1964, mediante una reacción multicomponente, lograron la síntesis de α–amidosulfonas empleando carbamato de etilo, formaldehído y sulfinato sódico en condiciones ácidas[15]. Más tarde, este mismo grupo de investigadores, extendió el estudio de esta metodología modificando la naturaleza tanto del derivado nitrogenado como del aldehído y la naturaleza del derivado de sulfinato sódico[16] (esquema 1.6), obteniendo en un solo paso los precursores de *N*-aciliminas.



X: O, S.
Z:-OEt, -CH_3,-Ph, -SEt, -$N(CH_3)_2$.
R :H,CH_3, Et.

R_1: H, Et, Ph.

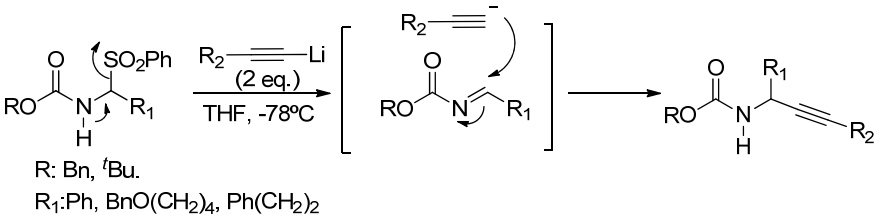
R_2: Et, Ph, 4-CH_3Ph

Esquema 1. 6

[14] Nájera, C.; Yus, M.*Tetrahedron* **1999**, *55*, 10547.
[15] Martin, S.F. *Acc. Chem. Res*. **2002**, *35*, 895.
[16] Engberts, J. B. F. N.; Strating, *J. Rec. Trav. Chim. Pays-Bas* **1965**, *84*, 942.

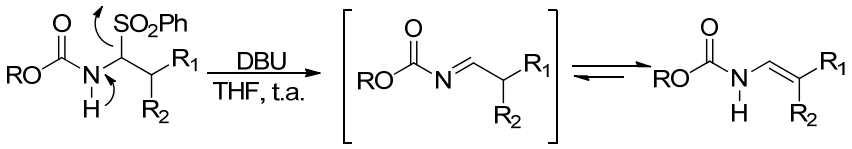
1.1.4. α–Amidosulfonas como precursores de *N*-aciliminas.

La eliminación de ácido bencenosulfónico en α–amidosulfonas, catalizada por medios básicos, permite la formación de *N*-aciliminas, que rápidamente reaccionan con agentes nucleófilos generando los correspondientes productos de adición. Este proceso puede ser considerado una reacción de eliminación-adición que aprovecha la doble naturaleza básica y nucleófila de algunos reactivos gracias a la cual el agente nucleófilo es lo suficientemente básico para realizar el paso de eliminación, por lo que un exceso de este agente conduce al producto de adición[17] (esquema 1.7).



Esquema 1. 7

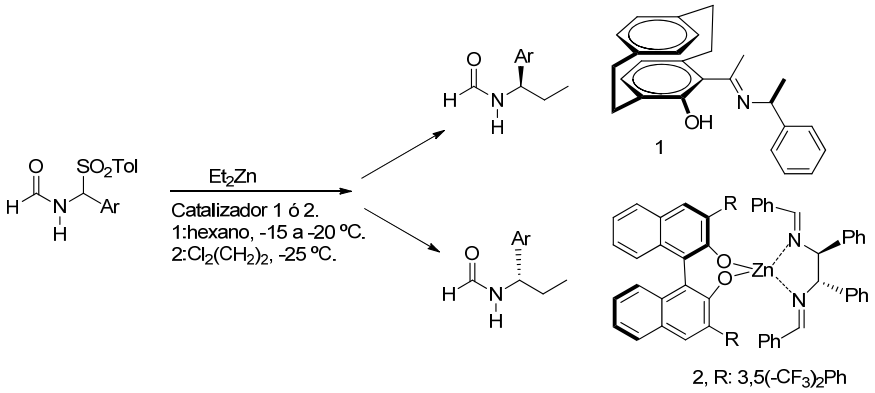
Por otro lado, el empleo de agentes con un pobre carácter nucleófilo, tal como el DBU, genera inicialmente la correspondiente *N*-acilimina que rápidamente tautomeriza a la correspondiente enamina, estable, con una marcada preferencia por el isómero Z[18] (esquema 1.8).



Esquema 1. 8

[17](a) Mecozzi, T.; Petrini, M. *J. Org. Chem*. **1999**, *64*, 8970. (b) Zhang, J.; Wei, C.; Li, C.; J. *Tetrahedron Lett.* **2002**, *43*, 5731.
[18]Mecozzi, T.; Petrini, M.; *Synlett*, **2000**, 73.

La reacción de α–amidosulfonas con heteronucleófilos o carbaniones permite obtener una gran variedad de aminoderivados. Este proceso puede transcurrir, además, de forma tanto diasteroselectiva como enantioselectiva[19] (esquema 1.9, tabla 1.1).



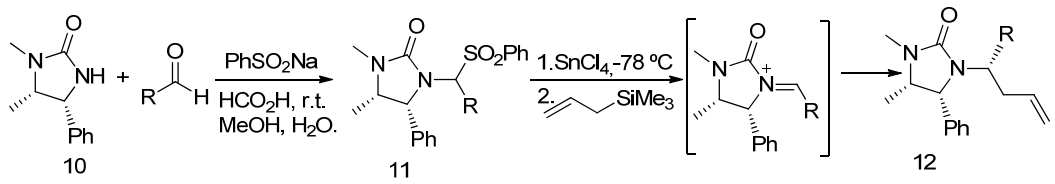
Esquema 1. 9

Entrada	Ar	Catalizador	Rdto.(%)	ee(%)
1	Ph	1	99	95(*R*)
2	Ph	2	91	83(*S*)
3	4-ClC_6H_4	1	99	89(*R*)
4	4-ClC_6H_4	2	80	90(*S*)
5	4-MeC_6H_4	1	99	95(*R*)
6	4-MeC_6H_4	2	78	86(*S*)

Tabla 1. 1

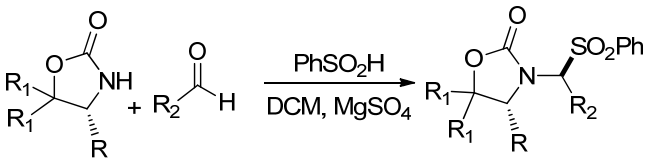
Continuando en la línea de síntesis asimétrica, el grupo de Pearson ha llevado a cabo la preparación de α-amidosulfonas quirales[20] (**11**) a partir de la imidazolin-2-onas (**10**) las cuales, en presencia de un ácido de Lewis, se transforman en los intermedios catiónicos de *N*-aciliminio sobre los que se da la adición de aliltrimetilsililo, dando lugar a la serie de imidazolin-2-onas (**12**) (esquema 1.10).

[19] Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940.
[20] Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622.



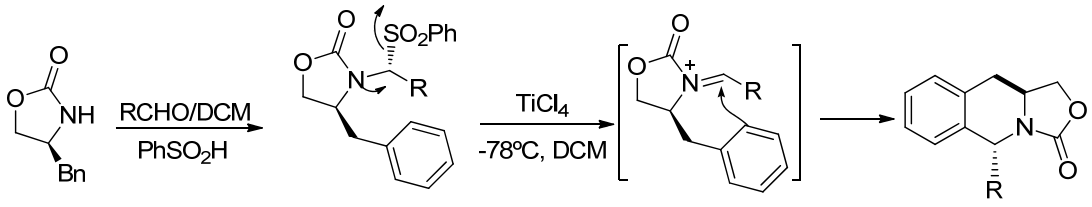
Esquema 1. 10

Aunque las condiciones generales de formación de sulfonas quirales fallan sobre las oxazolidin-2-onas, el grupo de Petrini ha aplicado una serie de modificaciones como son el uso del ácido sulfínico en medio apolar y la incorporación al medio de reacción de un agente deshidratante, como el sulfato de magnesio, que permiten dicha transformación[21] (esquema 1.11).



Esquema 1. 11

Las sulfonas quirales que provienen de 4-benciloxazolidin-2-onas en las que R = -CH_2Ph, pueden dar lugar a una reacción de ciclación intramolecular sobre el carbono *N*, *S*-acetal a través del intermedio de *N*-aciliminio, mediante el ataque nucleófilo por parte del fenilo en posición 4 (esquema 1.12)[22].



Esquema 1. 12

[21]Marcantoni, E.; Mecozzi, T.; Petrini, M; *J. Org. Chem*. **2002**, *67*, 2989.
[22]Mecozzi, T.; Petrini, M.; Profeta, R. *Tetrahedron: Asymmetry*, **2003**, *14*, 1171.

Aprovechando esta particular ciclación intramolecular, Petrini[23] ha desarrollado una ruta para acceder a la síntesis de aza-derivados de la podofilotoxina (figura 1.1), un agente antitumoral de origen natural que se emplea para el tratamiento de cáncer de pulmón, leucemia y cáncer genital.

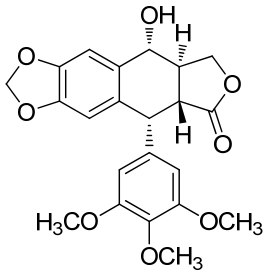
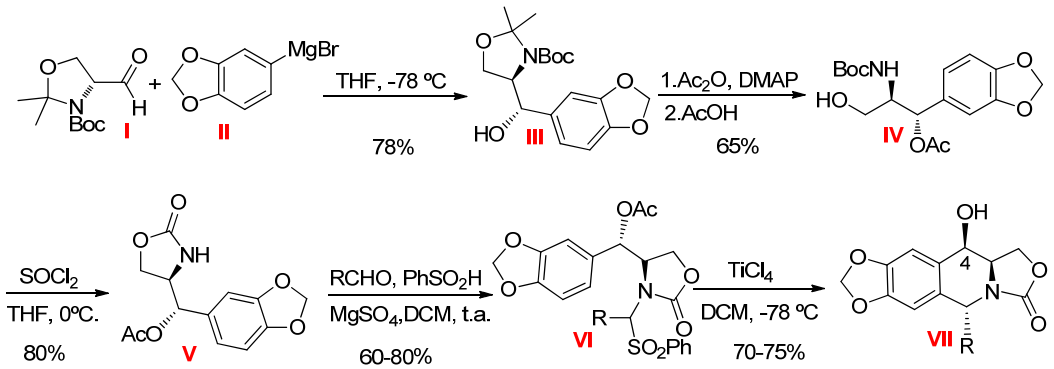


Figura 1. 1

Esta estrategia se ha aplicado también al compuesto **V**, que proviene de la reacción entre el llamado "aldehído de Garner" (**I**) y el magnesiano **II**. En el compuesto **III** que se origina, el grupo hidroxilo presenta una disposición *anti* con respecto al nitrógeno del anillo de oxazolidina, y su posterior acetilación seguida de la hidrólisis del aminal conduce al alcohol **IV** que es convertido en la oxazolidin-2-ona **V** por tratamiento con cloruro de tionilo. La aplicación de las condiciones de Petrini al compuesto **V** lo transforma en la correspondiente α–amidosulfona **VI**, que mediante el tratamiento con un ácido de Lewis conduce a los derivados triciclos **VII** de forma diasteroselectiva tras un proceso de epimerización del C-4 (esquema 1.13).



Esquema 1. 13

[23]Marcantoni, E.; Petrini, M.; Profeta, R. *Tetrahedron Lett.* **2004**, *45*, 2133.

Los tetraciclos así obtenidos contienen un núcleo de tetrahidroisoquinolina en su estructura, que procede de la ciclación intramolecular de un carbamato de feniletilo. Muchos compuestos de origen natural contienen en su núcleo esta estructura de THIQ, un ejemplo de estas son los alcaloides de la familia de las saframicinas, que comentaremos con más detalle en el siguiente apartado por su especial relevancia para nuestros objetivos.

1.2. Alcaloides derivados de tetrahidroisoquinolina y su relevancia como antitumorales.

1.2.1. Introducción.

Los antibióticos antitumorales pertenecientes a la familia de las tetrahidroisoquinolinas[24] incluyen potentes agentes citotóxicos. Entre ellos, se pueden considerar ejemplos representativos las saframicinas, procedentes de diversas cepas de *Streptomyces lavendulae*,[25] y una serie de compuestos de origen marino, como la jorumicina, aislada a partir de la babosa *Jorunna funebris*,[26] las renieramicinas, procedentes de diversas esponjas, principalmente *Reniera sp.* y *Xestospongia sp.*,[27] la cribrostatina, producida por esponjas del género *Cribochalina*,[28] y las ecteinascidinas, aisladas a partir del tunicado *Ecteinascidia turbinata*[29] (figura 1.2).

[24] Revisiones: a) Arai, T., Kubo, A. *The Alkaloids* (Brossi, A., Ed.), vol. 21, p. 55; Academic Press, **1983**. b) Remers, W. A., The Chemistry of Antitumour Antibiotics, vol. 2, pp. 93 y 120. Wiley, **1988**. c) Ozturk, T. *The Alkaloids* (Brossi, A., Ed.), vol. 53, p. 119. Academic Press, **2000**. d) Rinehart, K. L. *Med. Res. Rev.* **2000**, *20*, 1. e) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.

[25] Arai, T.; Takahashi, K.; Kubo, A. *J. Antibiot.* **1977**, *30*, 1015.

[26] Fontana, A.; Cavaliere, P.; Wahidulla, S.; Chandrakant, G. N.; Cimino, G. *Tetrahedron* **2000**, *56*, 7305.

[27] Suwanborirux, K.; Amnuoypol, S.; Plubrukarn, A.; Pummangura, S.; Kubo, A.; Tanaka, C.; Saito, N. *J. Nat. Prod.* **2003**, *66*, 1441.

[28] Pettit, G. R.; Collins, J. C.; Herald, D. L.; Doubek, D. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, D. L.; Tackett, L. P. *Can J. Chem.* **1992**, *70*, 1170.

[29] a) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Stroh, J. G.; Kieffer, P. A.; Sun, F.; Li, L. H.; Martin, D. G. *J. Org. Chem.* **1990**, *55*, 4512. b) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Stroh, J. G.; Kieffer, P. A.; Sun, F.; Li, L. H.; Martin, D. G. *J. Org. Chem.* **1991**, *56*, 1676.

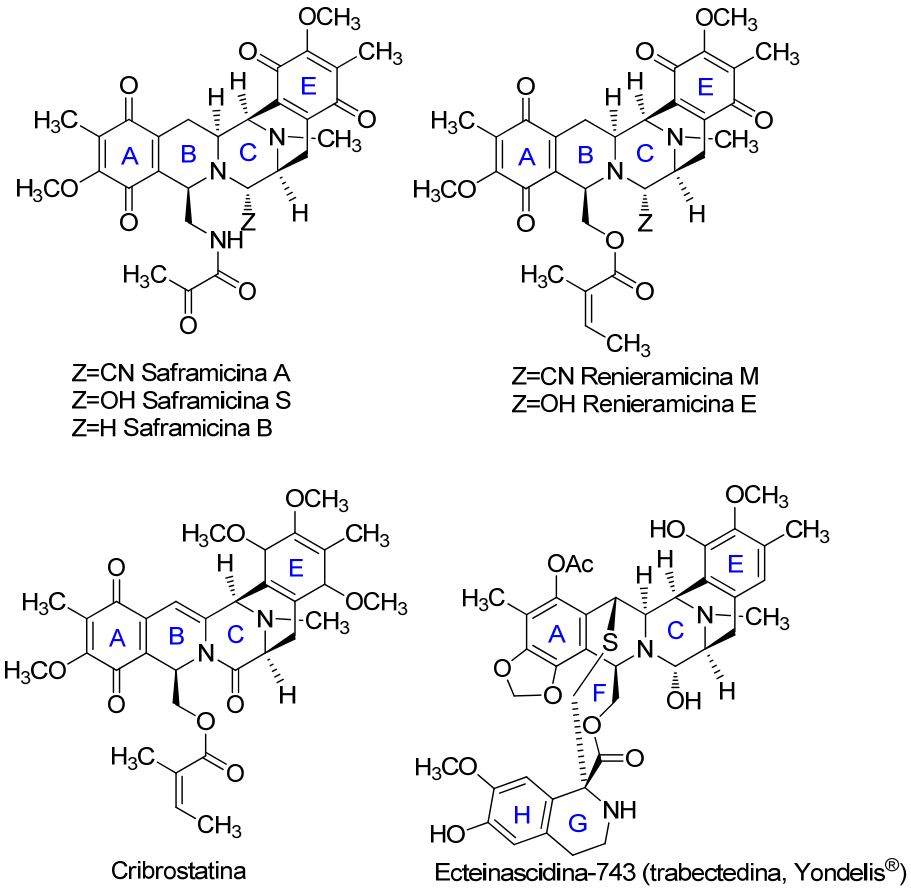


Figura 1. 2

Aunque todos estos alcaloides han demostrado actividad antitumoral, el de mayor interés actual es el compuesto de origen marino conocido como ecteinascidina 743 (Et-743, trabectedina, Yondelis®), desarrollada por la empresa española PharmaMar. Aunque existen cuatro síntesis totales de este producto natural[30], la complejidad de estos protocolos impide su aplicación industrial y ha obligado a resolver el problema del suministro de ecteinascidina 743 por semisíntesis a partir de la cianosafracina B, obtenida por fermentación de *Pseudomonas fluorescens*. No obstante, y a pesar de la semejanza entre

[30](a) Corey, E. J.; Gin, D. Y.; Kania, R. *J. Am. Chem. Soc.* **1996**, *118*, 9202. (b) Martínez, E. J., Corey, E. J. *Org. Lett.* **2000**, *2*, 993. (c) Nicolaou, K. C., Snyder, S. A. Classics in Total Synthesis II, capítulo 5. Wiley-VCH, **2003**. (d) Endo, A.; Yanagisawa, A.; Abe, M.; Toma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552. (e) Chen, J.; Chen, X.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2006**, *128*, 87. (f) Zheng, S.; Chan, C.; Furuuchi, T.; Wright, B. J. D.; Zhou, B.; Guo, J.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 1754.

ambas estructuras, la ruta semisintética es compleja, ya que consta de 22 pasos.[31] Por otra parte, ha sido posible simplificar la estructura de la ecteinascidina sin pérdida de actividad, como se ha demostrado con el desarrollo por Corey y Schreiber de la ftalascidina (figura 1.3), que presenta unas propiedades biológicas prácticamente idénticas a las de la ecteinascidina.[32]

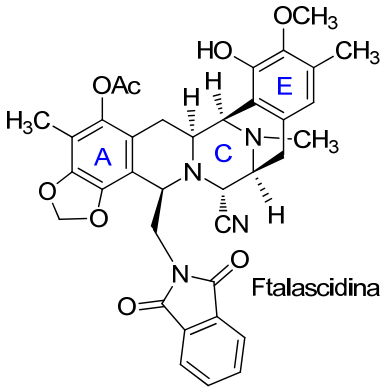


Figura 1. 3

Tanto las saframicinas como las ecteinascidinas se enlazan covalentemente al grupo 2-amino de restos de ácido desoxiguanílico en determinadas secuencias ricas en dicho nucleótido del surco menor del ADN (esquema 1.16).[33] Un estudio posterior ha demostrado que los aductos ADN-saframicina forman un complejo ternario con la gliceraldehído-3-fosfato deshidrogenasa (GADPH), lo que podría ser la causa última de la actividad antitumoral ya que esta enzima parece ser un coactivador de transcripción esencial para el inicio de la fase S del ciclo celular.[34] La relación entre GADPH y la actividad antitumoral de las saframicinas se confirma, además, porque la disminución de sus niveles lleva a la aparición de resistencia a estos antitumorales.

La unión saframicina-ADN es de tipo aminal y por tanto reversible, lo cual hace que la actividad dependa, además, de otras interacciones no covalentes, que tienen lugar principalmente a través de los anillos A y E. La alquilación del ADN requiere la formación

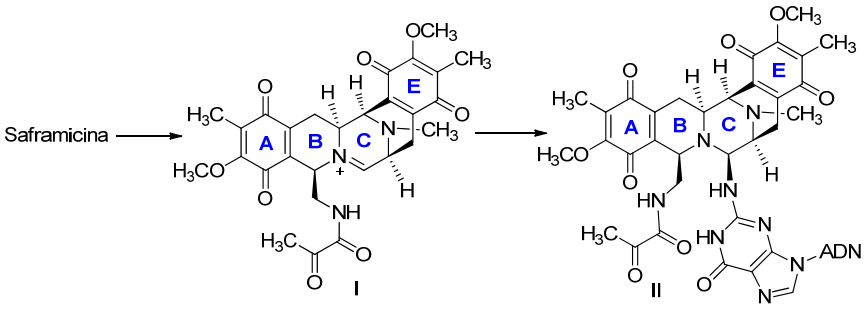
[31](a) Cuevas, C.; Pérez, M.; Martín, M. J.; Chicharro, J. L.; Fernández-Rivas, C., Flores, M.; Francesch, A.; Gallego, P.; Zarzuelo, M.; de la Calle, F.; García, J.; Polanco, C.; Rodríguez, I.; Manzanares, I. *Org. Lett.* **2000**, *2*, 2545. (b) Revisión de ésta y otras rutas de síntesis para las ecteinascidinas: Manzanares, I.; Cuevas, C.; García-Nieto, R.; Marco, E.; Gago, F. *Curr. Med. Chem. Anti-Cancer Agents* **2001**, *1*, 257.

[32](a) Martínez, E. J.; Owa, T.; Schreiber, S. L.; Corey, E. J. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 3496. (b) Martínez, E. J.; Corey, E. J.; Owa, T. *Chem. Biol.* **2001**, *8*, 1151.

[33]Zewail-Foote, M.; Hurley, L. H. *J. Am. Chem. Soc.* **2001**, *123*, 6485.

[34]Xing, C.; LaPorte, J. R.; Barbay, J. K.; Myers, A. G. *Proc. Nat. Acad. USA* **2004**, *101*, 5862.

del catión iminio **I**, por lo que la actividad es dependiente del carácter saliente del sustituyente del anillo C, siendo más activos (pero químicamente menos estables) los hidroxi derivados.



Esquema 1. 14

Es interesante destacar, no obstante, que la cribrostatina (figura 1.4) presenta una potente actividad contra nueve tipos diferentes de melanoma humano,[35] a pesar de presentar un carbonilo en la posición vecina a nitrógeno en la que otros compuestos tienen grupos salientes. Esto podría indicar la existencia de un proceso de bioactivación reductora, o bien un mecanismo de acción diferente, basado en el ataque directo de grupos nucleófilos de biomoléculas al extremo del sistema conjugado de esta molécula, quizá previamente activado por protonación del carbonilo quinónico conjugado con el nitrógeno gracias a la existencia de un doble enlace no presente en alcaloides relacionados.

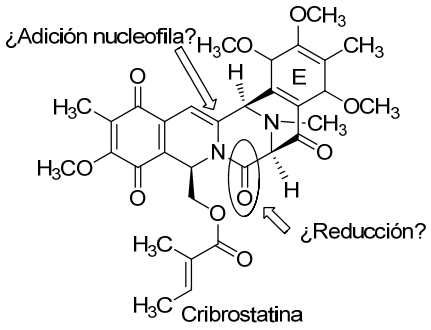
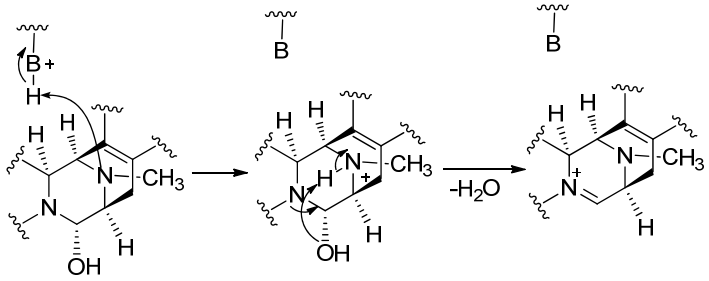


Figura 1. 4

[35]Kumar Jha, R.; Zi-rong, X. *Mar. Drugs* **2004**, *2*, 123.

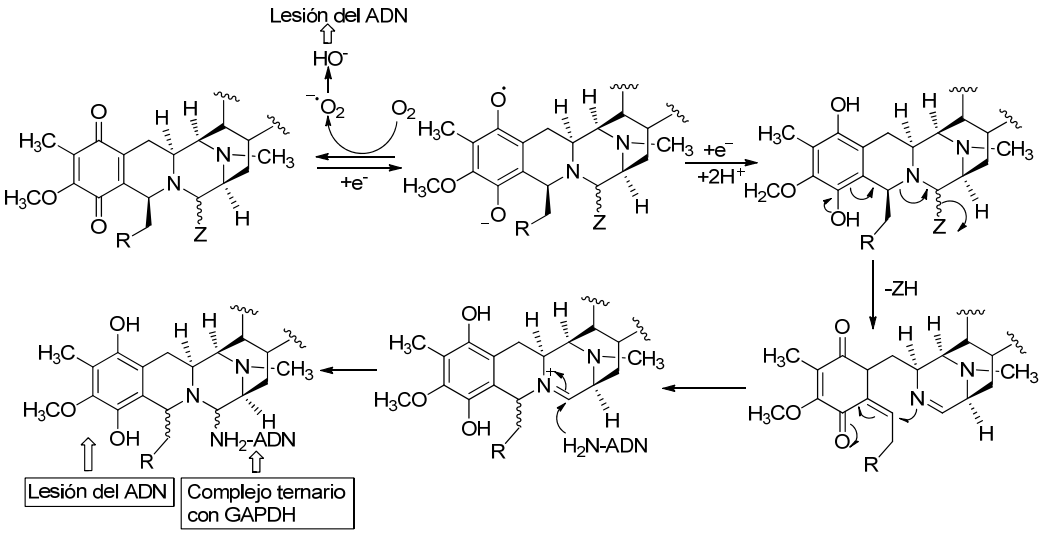
El segundo nitrógeno piperazínico, común a los anillos C y D (esquema 1.15), es importante para la actividad, ya que su protonación evita la del nitrógeno vecino al grupo saliente del anillo C, además de participar en enlaces de hidrógeno que explican la especificidad del reconocimiento de determinadas secuencias de bases.[36] También se ha sugerido su participación en el mecanismo de alquilación, al facilitar la expulsión del grupo hidroxilo en forma de agua.[37]



Esquema 1. 15

En el caso de las saframicinas, su naturaleza quinónica hace que puedan actuar generando radicales superóxido e hidroxilo, que contribuyen a su acción citotóxica en ambientes aerobios.[38] Por otra parte, diversos estudios han demostrado que la actividad antitumoral de las saframicinas aumenta en presencia de agentes reductores, por lo que es posible la existencia de un mecanismo de alquilación reductora con participación de un hidroxilo de hidroquinona.[39] (esquema 1.16)

[36]Seaman, F. C.; Hurley, L. H. *J. Am. Chem. Soc.* **1998**, *120*, 13028.
[37]Moore, R. M.; Seaman, F. C.; Wheelhouse, R. T.; Hurley, L. H. *J. Am. Chem. Soc.* **1998**, *120*, 2490.
[38]Lown, J. W.; Joshua, A. V.; Lee, J. S. *Biochemistry* **1982**, *21*, 419.
[39](a) Ishiguro, K.; Sakiyana, S.; Takahashi, K.; Arai, T. *Biochemistry* **1978**, *17*, 2545. (b) Ishiguro, K.; Takahashi, K.; Yazawa, K.; Sakiyana, S.; Arai, T. *J. Biol. Chem*. **1981**, *256*, 2162. (c) Hill, G. C.; Remers, W. A. *J. Med. Chem*. **1991**, *34*, 1990.



Esquema 1. 16

Se ha comprobado que algunos análogos de saframicina con estructura de bis-hidroquinona son mucho más activos que el producto natural, presentando algunos de ellos una elevadísima actividad frente a sarcoma humano.[40] Sin embargo, no existe un estudio sistemático de la influencia del carácter aceptor o donador electrónico de los sustituyentes en los anillos A y E de las saframicinas en su actividad como consecuencia de una mayor o menor facilidad de reducción, y por otra parte hay que tener en cuenta que algunos análogos de las saframicinas no tienen la posibilidad de reducirse a quinona, como la ftalascidina y aun así presentan actividades antitumorales muy potentes.

La información disponible actualmente acerca de las relaciones entre estructura y actividad antitumoral de análogos de ecteinascidina y ftalascidina es relativamente escasa por estar limitada a compuestos semisintéticos obtenidos a partir de productos de fermentación o a intermedios de síntesis totales. Se han realizado, no obstante, algunos estudios acerca de la simplificación de la estructura de las saframicinas, demostrándose que el fragmento tricíclico ABC es en general insuficiente, aunque algunos análogos con el anillo C pirrólico poseen actividad antifúngica[41] y otros han mostrado cierta actividad antitumoral.[42] Por otra parte, el fragmento ABCD parece suficiente para la actividad, ya que corresponde

[40]Myers, A. G.; Plowright, A. T. *J. Am. Chem. Soc.***2001**, *123*, 5114.

[41](a) Kubo, A.; Nakai, T.; Koizumi, Y.; Saito, N.; Mikami, Y.; Yazawa, K.; Uno, J. *Heterocycles***1992**, *34*, 1201. (b) Kubo, A.; Nakai, T.; Koizumi, Y.; Kitahara, Y.; Saito, N.; Mikami, Y.; Yazawa, K.; Uno, J. *Heterocycles***1996**, *42*, 195.

[42]Irene Ortín Remón. Trabajo para la obtención del Diploma de Estudios Avanzados. Universidad Complutense, **2007**.

a la estructura de las quinocarcinas, otro grupo de alcaloides tetrahidroisoquinolínicos que han despertado gran interés como agentes antitumorales a partir de 1985, tras la demostración en el NCI de su especificidad *in vitro* frente a melanomas,[43] lo que ha llevado a la evaluación clínica de algunos análogos de este compuesto.[44]

La equivalencia previamente mencionada entre la ecteinascidina y la ftalascidina se atribuye a que la cadena lateral de este último compuesto adopta una conformación superponible con la de los anillos FGH de la ecteinascidina. En este sentido, cabe mencionar también que la cadena lateral de las saframicinas desempeña también un papel importante en su actividad,[45] que no se ha explicado adecuadamente.

1.3. Métodos de síntesis de saframicinas: ruta de formación de los anillos ACE-D-B.

Existen varias revisiones bibliográficas recientes que recopilan los métodos desarrollados para la síntesis de alcaloides derivados de tetrahidroisoquinolina[46]. En este apartado nos limitaremos a resumir brevemente algunas rutas que utilizan 2,5-piperazinadionas como materiales de partida, para situar nuestro trabajo en su contexto.

La primera síntesis de la saframicina A (esquema 1.17) se debe a Fukuyama.[47] Se inició con la condensación en medio básico entre la 1,4-diacetil-2,5-piperazinadiona **I** y el aldehído **II** para dar el compuesto **III**. Su hidrogenación catalítica a alta presión condujo a la reducción de su doble enlace junto con la desprotección del hidroxilo fenólico. La reprotección de éste en forma de silil éter y la introducción de un grupo benciloxicarbonilo en el nitrógeno completaron la preparación de **IV**, que proporcionó **V** tras una nueva condensación aldólica con el aldehído **II**. La reducción selectiva del grupo *N*-Cbz dio lugar a un hemiaminal intermedio, cuyo tratamiento con ácido fórmico condujo a su ciclación a **VI**, con un catión aciliminio como intermedio y tras una etapa de desprotección del silil éter. La hidrogenación a alta presión del doble enlace de **VI** transcurrió con desprotección simultánea del grupo *N*-Cbz, que se metiló a **VII** con formaldehído en condiciones reductoras. La creación del anillo B se llevó a cabo por reducción del sistema de lactama

[43](a) Chiang, C. D.; Kanzawa, F.; Matsushima, Y.; Nakano, H.; Takahashi, H.; Terada, M.; Morinaga, S.; Tsuchiya, R.; Sasaki, Y., *J. Pharmacobiodyn.***1987**, *10*, 431. (b) Inaba, S.; Shimoyama, M., *Cancer Res.***1988**, *48*, 6029. (c) Kanamaru, R.; Konishi, Y.; Ishioka, C.; Kakuta, H.; Sato, T.; Ishikawa, A.; Asamura, M.; Wakui, A. *Cancer Chemother. Pharmacol.***1988**, *22*, 197.

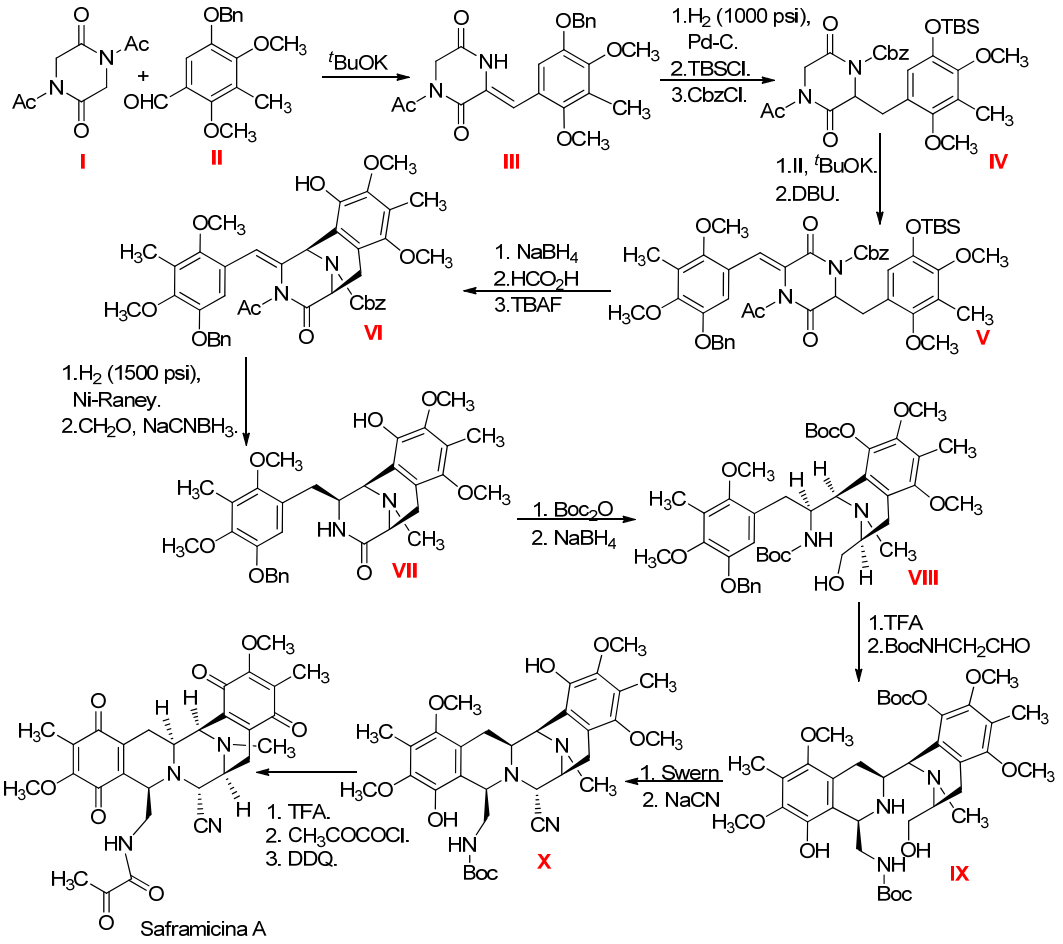
[44]Plowman, J.; Dykes, D. J.; Narayanan, V. L.; Abbott, B. J.; Saito, H.; Hirata, T.; Grever, M. R., *CancerRes*. **1995**, *55*, 862.

[45]Kaneda, S.; Hour-Young, C.; Yazawa, K.; Takahashi, K.; Mikami, Y.; Arai, T. *J. Antibiot.***1987**, 1640.

[46](a)Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002,** *102,* 1669-1730. (b) Avendaño, C.; de la Cuesta, E. *Chem. Eur. J.***2010**, *16*, 9722.

[47]Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am. Chem. Soc*. **1990**, *112*, 3710.

del *N*-Boc derivado de **VII**, que condujo a **VIII**. La desprotección del grupo carbamato condujo a una amina, sobre la que se llevó a cabo una ciclación de Pictet-Spengler, que proporcionó **IX**, compuesto sobre el que volvió a crearse el anillo C por oxidación de su hidroxilo primario a aldehído, que permitió el ataque por el grupo amino liberado a partir del sustituyente *N*-Boc existente en el anillo B. Esta reacción se realizó en presencia de cianuro sódico, que transformó el hemiaminal intermedio resultante de dicho ataque en el nitrilo **X**, que ya contiene el sistema pentacíclico completo de la saframicina. La síntesis se completó por la introducción de la cadena de piruvilo en el nitrógeno, previa desprotección, y una etapa final de oxidación a quinona de los dos anillos aromáticos.

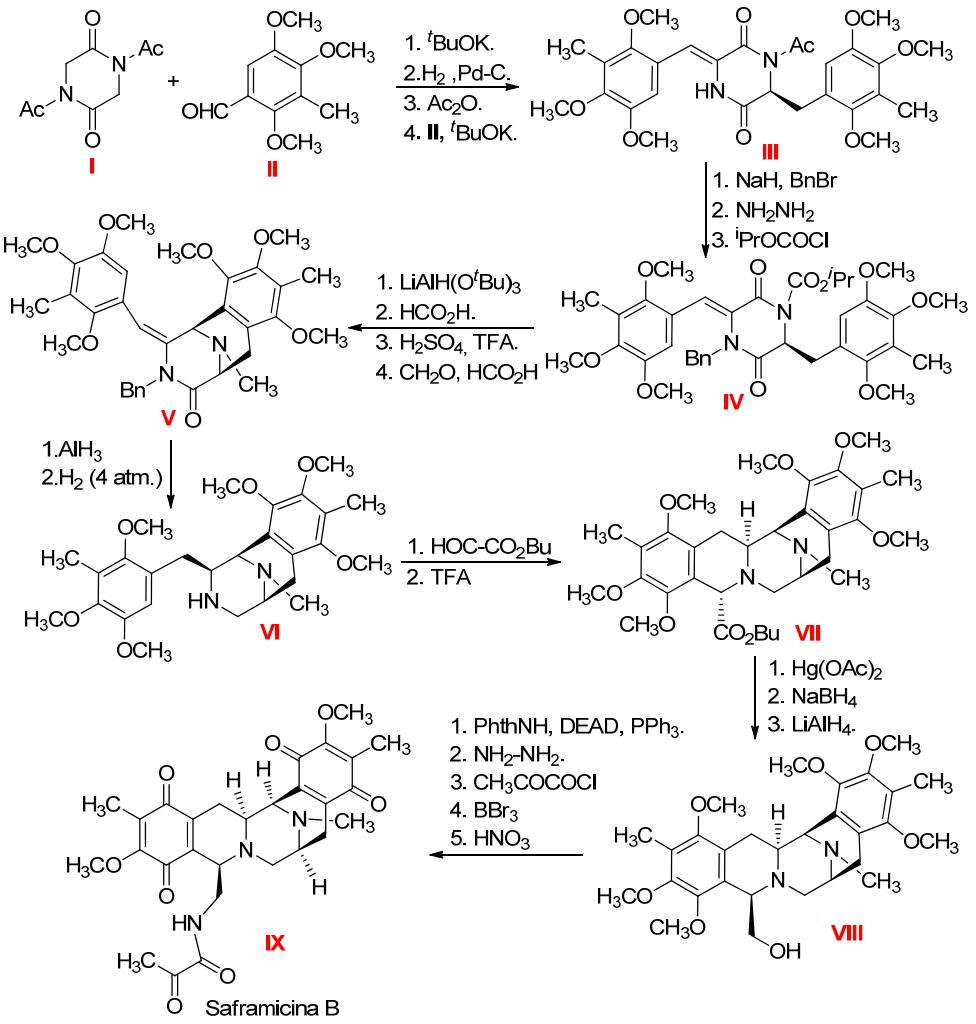


Esquema 1. 17

En la síntesis de la saframicina B de Kubo[48] (esquema 1.18), se obtuvo el compuesto **III** (semejante al intermedio **V** de Fukuyama) en cuatro pasos a partir de la 1,4-diacetil-2,5-piperazinadiona y el aldehído **II**. Para conseguir la activación selectiva del nitrógeno 1 de este compuesto, se protegió el nitrógeno 4 por introducción de un grupo bencilo, antes de desacetilar N-1 e introducir sobre él un grupo isopropiloxicarbonilo. La reducción del compuesto **IV** así obtenido con hidruro de litio y tri-*terc*butoxialuminio proporcionó el correspondiente hemiaminal, que se cicló por tratamiento con ácido, procediéndose a continuación a la hidrólisis del grupo carbamato y su sustitución por un metilo, en condiciones de Eschweiler-Clarke, resultando el compuesto **V**.

Es interesante destacar que el doble enlace de **V** presentó una configuración *E*, pudiendo atribuirse su isomerización al medio ácido empleado en la ciclación y a la interacción repulsiva entre el grupo *N*-bencilo y el arilo en la estructura *Z*. Puesto que la saframicina B no está funcionalizada en el anillo C, se redujo el sistema de lactama y a continuación se eliminó el grupo bencilo por hidrogenolisis, resultando la amina **VI**. Su ciclación en condiciones de Pictet-Spengler con glioxilato de butilo condujo a **VII**, con la configuración del estereocentro del anillo B opuesta a la del producto natural. Para corregirla, se oxidó este anillo a piridinio por tratamiento con acetato de mercurio (II) y se redujo a continuación con borohidruro sódico, produciéndose el ataque del hidruro por la cara inferior, menos impedida. La reducción del grupo éster condujo a **VIII**, que se transformó, finalmente, en la saframicina B tras una secuencia de cinco pasos.

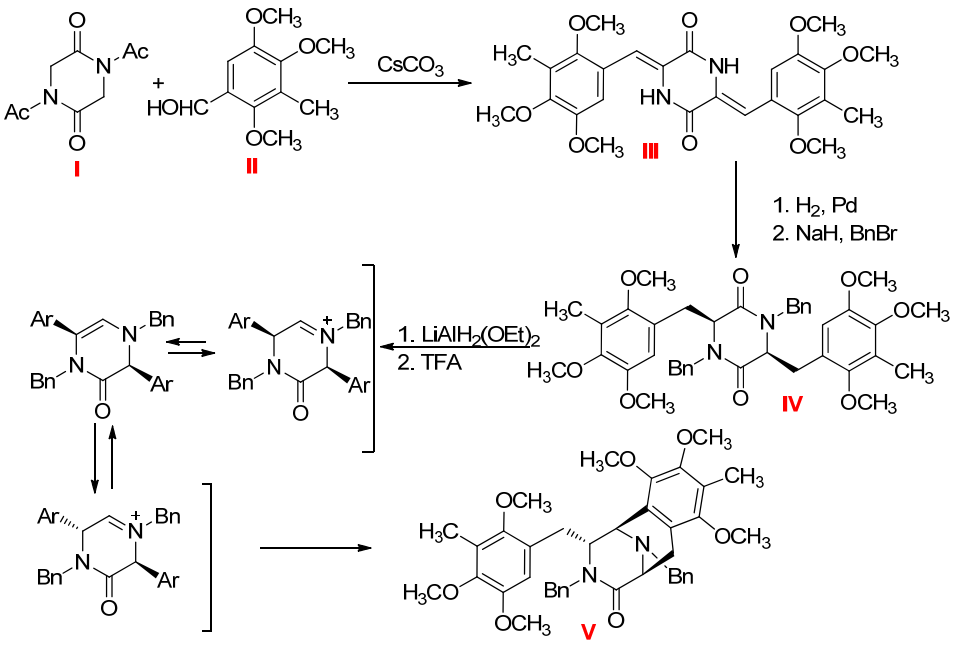
[48] a) Kubo, A.; Saito, N.; Yamauchi, R.; Sakai, S. *Chem. Pharm. Bull.***1987**, *35*, 2158. b) Kubo, A.; Saito, N.; Yamato, H.; Kawanami, Y. *Chem. Pharm. Bull.***1987**, *35*, 2525. c) Kubo, A.; Saito, N.; Nakamura, M.; Ogata, K.; Sakai, S. *Heterocycles***1987**, *26*, 1765. d) Kubo, A.; Saito, N.; Yamato, H.; Yamauchi, R.; Hiruma, K.; Inoue, S. *Chem. Pharm, Bull.***1988**, *36*, 2607. e) Kubo, A.; Saito, N.; Yamato, H.; Masubichi, K.; Nakamura, M.; *J. Org. Chem.***1988**, *53*, 4295.



Esquema 1. 18

En un intento de reducir el número de pasos de este tipo de secuencias, Liebeskind preparó el compuesto **III** por medio de una condensación doble. La hidrogenación catalítica de **III**, seguida de una bencilación doble, condujo al compuesto **IV**. El paso clave de la secuencia de Liebeskind consistió en la reducción selectiva de uno de los carbonilos de **IV**, lo que permitió su ciclación. Desgraciadamente, esta reacción fue acompañada por la epimerización del estereocentro vecino al grupo bencilo que no participa en la ciclación y dio lugar al compuesto **VIII**, presumiblemente a través de la serie de equilibrios

representada en el esquema 1.19. Todos los intentos de corregir esta esteroquímica no deseada fueron infructuosos.[49]



Esquema 1. 19

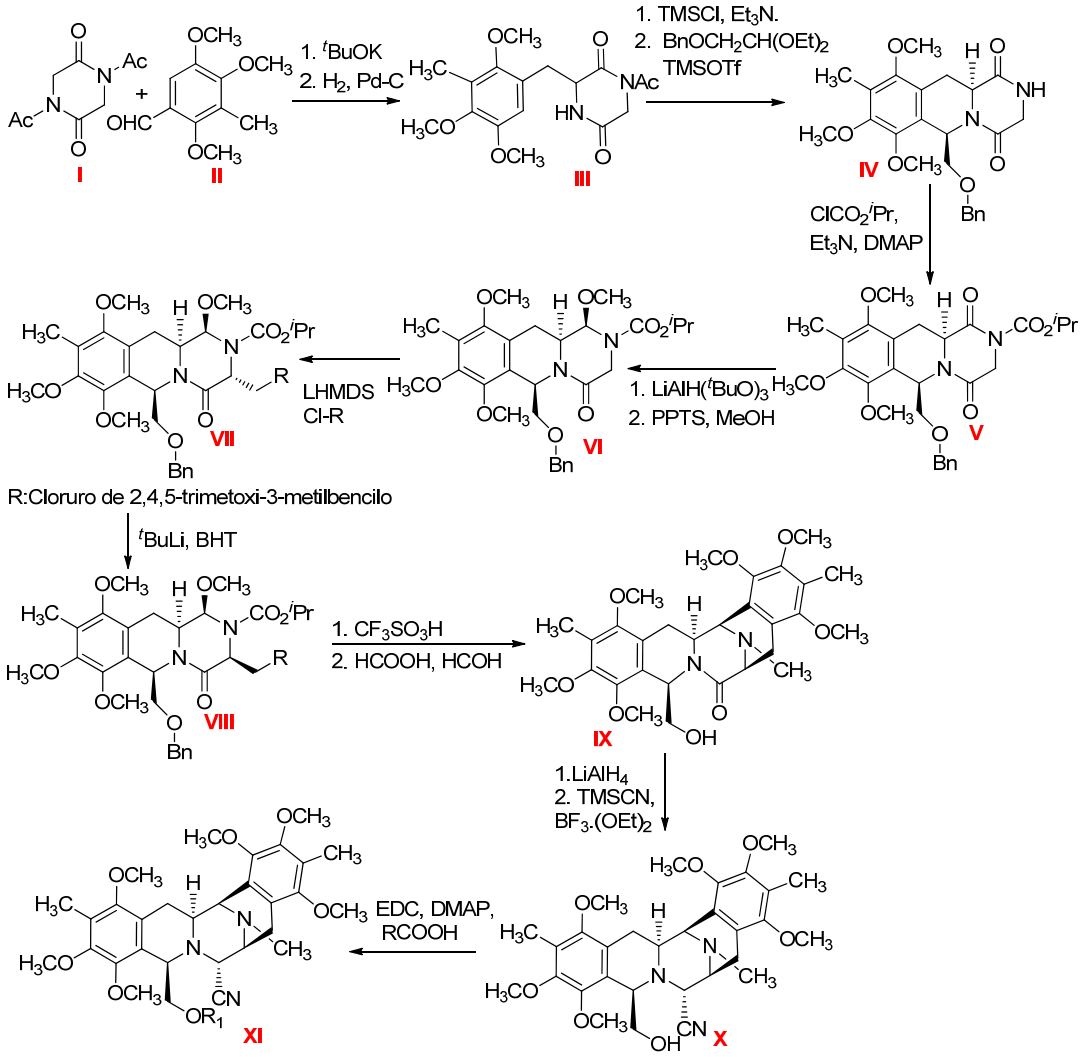
1.4. Síntesis siguiendo la secuencia de formación de anillos ACE-B-D.

Una aproximación apenas explotada es el uso del sistema de pirazino[1,2-*b*]isoquinolina, que contiene los anillos A-C, como intermedio clave. Esta estrategia fue seguida por el grupo de Avendaño[50] para la obtención de análogos de la saframicina (esquema 1.20). Mediante una monocondensación y posterior reducción catalítica se alcanzó el compuesto **III**, que fue sometido a una ciclación de tipo Pictet Spengler dando lugar a los sistemas pirazino[1,2-*b*] isoquinolina, con la estereoquímica deseada. A continuación, se aumentó la electrofilia de C1 con la formación del carbamato, **V**. Este compuesto se sometió a una reducción con un donador de hidruro, obteniéndose el correspondiente hemiaminal, que se transformó en **VI**. Aprovechando la acidez del H3 y mediante el uso de la hexametildisilazida de litio, se llevó a cabo una alquilación con cloruro de 2,4,5-trimetoxi-3-metilbencilo para obtener el compuesto **VII**, con una configuración en C3 inversa a la

[49]Shawe, T. T.; Liebeskind, L. S. *Tetrahedron* **1991**, *47*, 5643.

[50](a) Ortín, I.; González, J. F.; De la Cuesta, E.; Avendaño, C. *Bioorg. Med. Chem.* **2010**, *18*, 6813. (b) Ortín, I.; González, J. F.; De la Cuesta, E.; Avendaño, C. *Tetrahedron* **2009**, *65*, 2201. (c) Ortín, I.; González, J. F.; Manguán-García, C.; Perona, R.; de la Cuesta, E.; Avendaño, C. *Bioorg. Med. Chem.* **2008**, *16*, 9065.

perseguida. La epimerización de este centro transcurre con la formación del enolato y posterior donación de un protón por parte del butilhidroxitolueno, bajo el control estérico del resto de los sustituyentes de la molécula. El compuesto **VIII** así formado se trató con un superácido, lográndose obtener el pentaciclo y la posterior aplicación de una formilación reductora llevó a la metilación del nitrógeno de amina. La cianación transcurrió a través de un intermedio de oxazolidina que, en presencia de un ácido de Lewis y un donador de cianuro, rinde **X**. Por último, la esterificación del sustituyente hidroxi en C6 en presencia de dimetilaminopiridina y una carbodiimida, ofrece el compuesto **XI**.

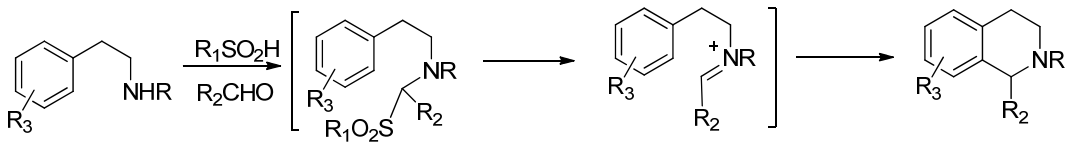


Esquema 1. 20

2. Capitulo 2: Objetivos.

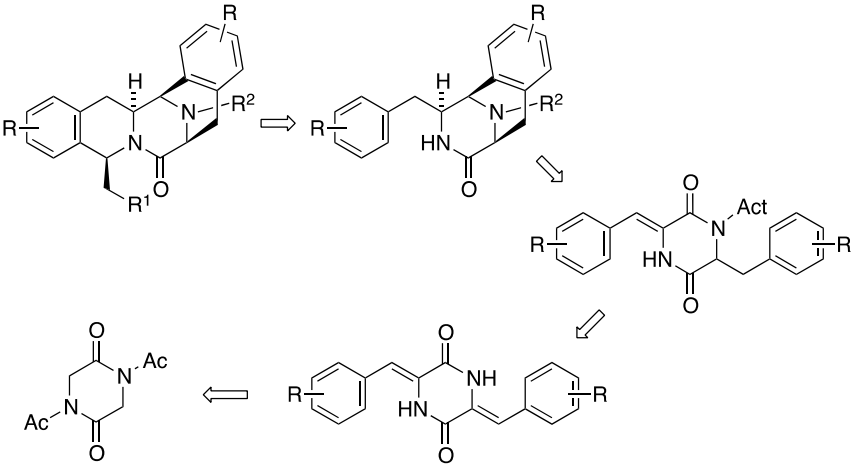
Muchas y variadas son las metodologías empleadas en la obtención del sistema pentacíclico de las saframicinas y aun así sigue siendo necesario un planteamiento que nos acerque a síntesis simplificadas. Un examen de las estructuras de estos alcaloides revela que muchos de ellos están constituidos por dos unidades idénticas de tetrahidroisoquinolina unidas a un ciclo central de piperazina. Esta simetría oculta proporciona la posibilidad de diseñar rutas sintéticas simplificadas basadas en el empleo de materiales de partida simétricos, y el objetivo principal de esta tesis es la exploración de dos estrategias de este tipo. A continuación se detallan algunos objetivos más específicos.

1). El paso determinante en un número importante de rutas sintéticas descritas para la obtención de saframicinas pasa por la formación de anillos de tetrahidroisoquinolina. Uno de nuestros objetivos es la puesta a punto de un método de obtención de este sistema heterocíclico mediante el empleo de α-amidosulfonas como intermedios, así como un estudio que nos permita establecer el alcance de la reacción y sus posibles limitaciones.



Esquema 2. 1

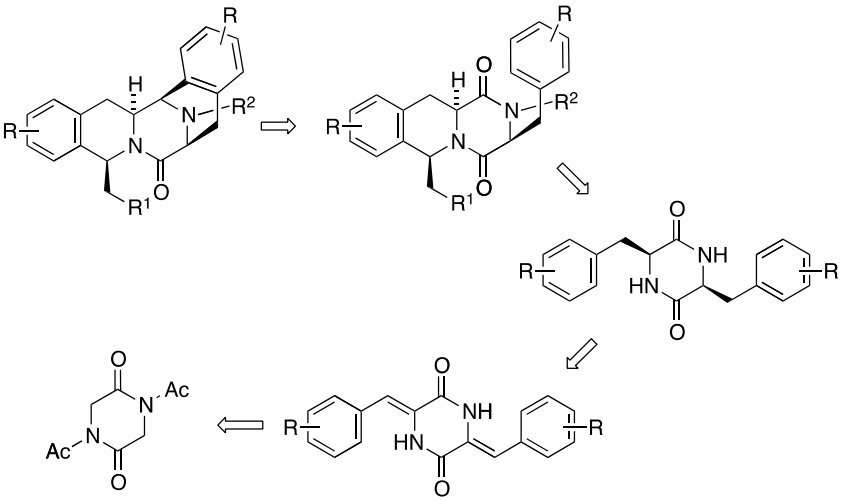
2). Ruptura de la simetría de derivados de 3,6-bis(arilmetilen)-2,5-piperazinadiona por reducción selectiva y construcción de los sistemas pentacíclicos creando en último lugar el



Esquema 2. 2

anillo B mediante el empleo de intermedios de α-amidosulfona.

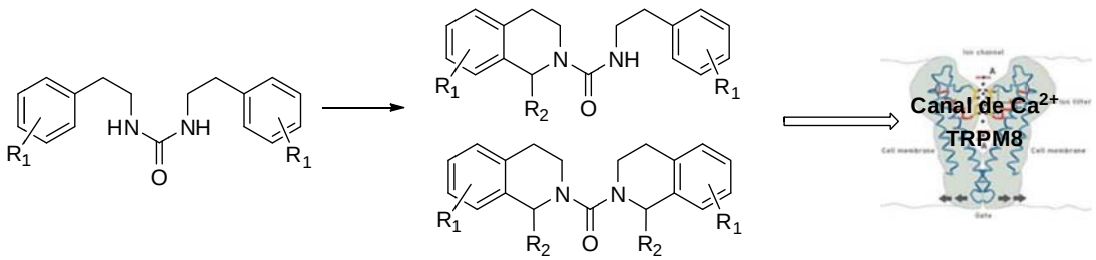
3).Estudio de una segunda ruta basada en la simetría inherente a las saframicinas, basada en la construcción inicial del anillo B por aplicación de la química de α-amidosulfonas y la generación del anillo D como etapa final.



Esquema 2. 3

4) Los objetivos anteriores requieren resolver el problema de lograr la configuración correcta del estereocentro del anillo B y, además, desarrollar una metodología que nos permita introducir variedad estructural en la posición C9 de las saframicinas.

2.-Búsqueda de nuevos prototipos que contengan estructuras de tetrahidroisoquinolina como ligandos de canales de calcio TRPM8 como dianas terapéuticas en el desarrollo de antitumorales y estudio de relación estructura-actividad de los derivados sintetizados.



Esquema 2. 4

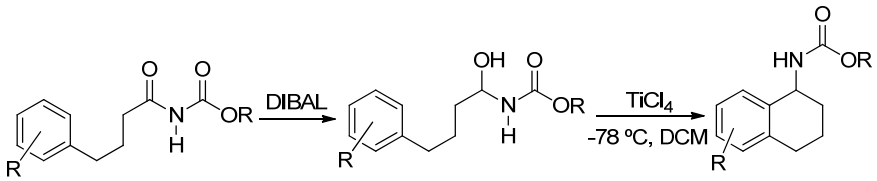
3. Capítulo 3: Resultados y discusión

3.1. Estudio de la obtención de tetrahidroisoquinolinas a través de intermedios de α-amidosulfonas.

3.1.1. Antecedentes.

Una gran variedad de estrategias sintéticas han perseguido la obtención de tetrahidroisoquinolinas debido a su implicación en la estructura de compuestos biológicamente activos. Centraremos este apartado en métodos basados en la formación como intermedio de un catión aciliminio derivado de un carbamato.

La inestabilidad de los cationes aciliminio[51] lleva a la necesidad de diseñar reacciones donde dicho intermedio adquiera una reactividad controlable, con el fin de poder alcanzar los productos deseados. De esta forma DeNinno *et al.*[52] realizaron por primera vez ciclaciones intramoleculares a partir de *N*-acilcarbamatos que, tras una reducción del grupo acilo, condujeron a *N*-hemicarbamatos estables. A continuación, el empleo de ácidos de Lewis[53] dio lugar a la ciclación correspondiente, a través del ataque nucleófilo por parte del anillo aromático (esquema 3.1). Esta reacción abre la puerta a la posibilidad de obtención de *N*-aciliminios cuya reactividad pueda ser dirigida.



Esquema 3. 1

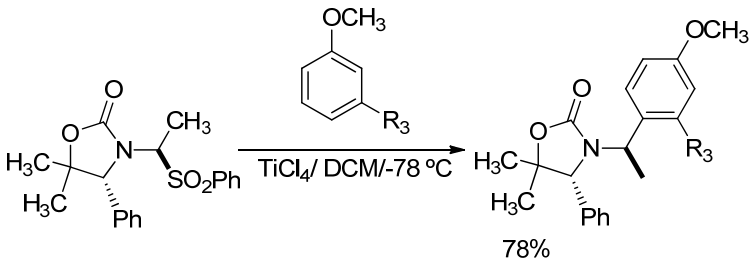
Un nuevo método para la generación de aciliminios derivados de carbamatos nace en el grupo de Petrini,[54] que mediante la formación de α-amidosulfonas hace posible la activación de la posición α al nitrógeno de carbamatos ciclicos a través de un intermedio de aciliminio (esquema 3.2). Hay que destacar la necesidad de emplear tetracloruro de

[51] Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron,* **1975**, *31*, 1437.

[52] DeNinno M. P.; Eller C.; Etienne J. B. *J. Org. Chem.* **2001,** *66,* 6988.

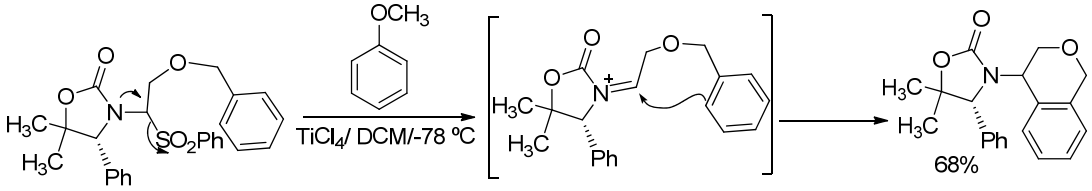
[53] (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985***, 41,* 4367. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

titanio como catalizador y el hecho de que esta reacción está limitada al uso de sistemas aromáticos activados.



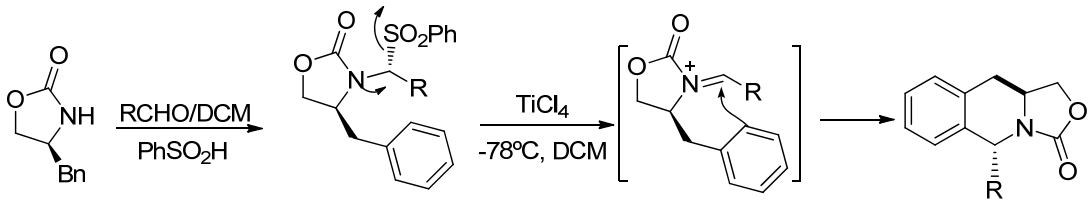
Esquema 3. 2

Este tipo de reacciones intermoleculares no tienen lugar cuando compiten con un ataque nucleófilo intramolecular alternativo, aunque de nuevo es necesario el empleo de un ácido de Lewis (esquema 3.3).



Esquema 3. 3

El primer ejemplo en la obtención de tetrahidrisoquinolinas[22] surge de la aplicación de esta metodología a carbamatos cíclicos en presencia del correspondiente aldehído y ácido bencenosulfínico (esquema 3.4). Posteriormente, este tipo de reacciones han sido usadas en la síntesis de aza-análogos de la podofilotoxina[55] (ver también el apartado 1.1.4).

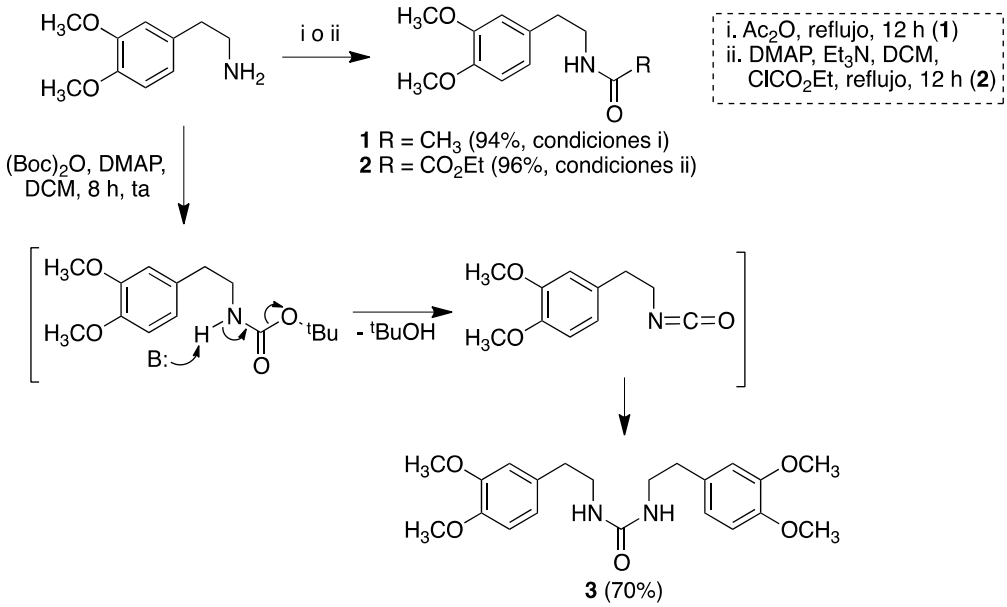


Esquema 3. 4

[55]Marcantoni, E.; Petrini, M.; Profeta, R. *Tetrahedron Lett.* **2004**, *45*, 2133.

3.1.2. Aplicación de α-amidosulfonas a una síntesis generalizada de tetrahidroisoquinolinas.

Con estos antecedentes, decidimos establecer unas condiciones generales de obtención de THIQs partiendo de fenetilaminas en las que la amina presenta distintos sustituyentes de tipo acilo. Como materiales de partida iniciales, obtuvimos en primer lugar el acetil derivado y el carbamato de etilo procedentes del compuesto comercial homoveratrilamina. También preparamos el derivado de urea correspondiente por tratamiento de la homoveratrilamina con pirocarbonato de di*terc*butilo en presencia de una cantidad equimolecular de 4-dimetilaminopiridina, en un proceso que presumiblemente tiene un isocianato como intermedio (esquema 3.5).



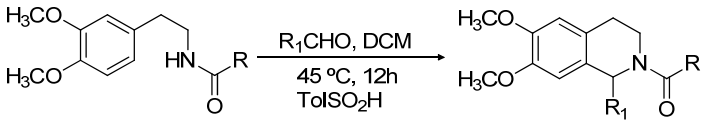
Esquema 3. 5

Partiendo de estos compuestos, aplicamos las condiciones de Petrini *et al.*[56] para alcanzar los intermedios correspondientes de tipo α-amidosulfona. El ácido sulfínico que usamos en nuestras reacciones fue el ácido *para*-toluenosulfínico, **4**. En nuestro caso fue necesaria una ligera elevación de la temperatura para conseguir que la reacción tuviera lugar, ofreciéndonos estas nuevas condiciones, una ciclación directa a los sistemas de THIQs **5**-**7** con excelentes rendimientos en general (esquema 3.6, tabla 3.1), y sin necesidad de

[56] Mataloni, M.; Petrini M.; Profeta R. *Synlett*, **2003**, *8,* 1129.

emplear ácidos de Lewis ni de aislar la sulfona intermedia. Una ciclación relacionada en la que no se aísla el intermedio de α-amidosulfona ya había sido documentada por el grupo de Frey[57], aunque con un rendimiento de tan solo el 4%.

Los aldehídos empleados en la reacción de formación de THIQs son comerciales, a excepción del *p*-hidroxibenzaldehído, compuesto **8**, que se sintetiza fácilmente a partir de *p*-(hidroximetil)fenol por oxidación con IBX.



Esquema 3. 6

Compuesto	R_1-	R-	Rdto.%
5a	2-naftil	CH_3CH_2O	99
5b	C_3H_7	CH_3CH_2O	89
5c	*p*-$NO_2C_6H_4OC_6H_4$	CH_3CH_2O	88
5d	*o*-ClC_6H_4	CH_3CH_2O	75
5e	*p*-BrC_6H_4	CH_3CH_2O	75
5f	*o*-BrC_6H_4	CH_3CH_2O	90
5g	*o*-$NO_2C_6H_4$	CH_3CH_2O	69
5h	*m*-$NO_2C_6H_4$	CH_3CH_2O	83
5i	3,4-$(CH_3O)_2C_6H_3$	CH_3CH_2O	88
5j	2,5-$(CH_3O)_2C_6H_3$	CH_3CH_2O	79
5k	2,4-$(CH_3O)_2C_6H_3$	CH_3CH_2O	41
5m	2,4,5-$(CH_3O)_2C_6H_3$	CH_3CH_2O	57
5n	Ph	CH_3CH_2O	56
5o	C_2H_5	CH_3CH_2O	97
5p	*p*-HO-C_6H_4	CH_3CH_2O	80
6	(a)C_2H_5	CH_3	45
7e	C_2H_5	3,4-$(CH_3O)_2C_6H_3(CH_2)_2NH$	64
7b	*m*-$NO_2C_6H_4$	3,4-$(CH_3O)_2C_6H_3(CH_2)_2NH$	85

(a)El máximo rendimiento de esta reacción se consigue a las 156h de reacción.

Tabla 3. 1

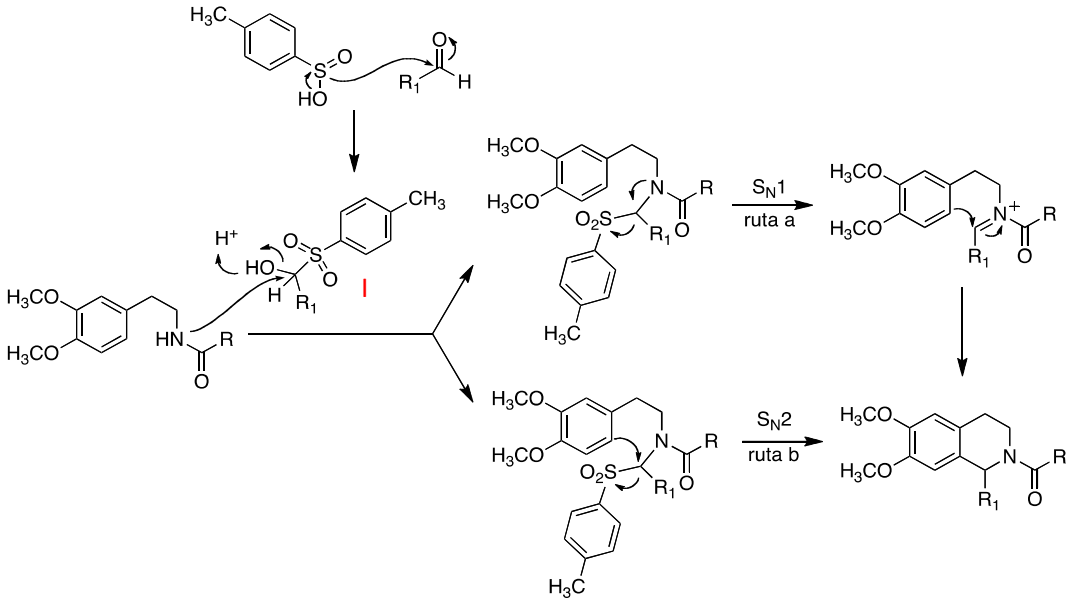
[57] Tussetschläger, S.; Angelika, B.; Laschat, S.; Frey, W. *Eur. J. Org. Chem.* **2007**, *33,* 5590.

De los datos de la tabla 3.1, se puede deducir que la nucleofilia de los diferentes nitrógenos de los compuestos de partida determina su reactividad, siendo más reactivo el carbamato (**1**) que la urea (**3**) y ésta más que la amida (**2**), como queda reflejado en los rendimientos obtenidos para los compuestos **5o** (97 %), **7e** (64 %) y **6** (45 %) respectivamente (esquema 3.7).

Del comportamiento de los aldehídos en la reacción podemos concluir, que el efecto donador o aceptor de electrones de los sustituyentes sobre los anillos aromáticos no influye en la reactividad de los aldehídos (88 % de rendimiento para los compuestos **5c** y **5i**), siendo únicamente el efecto estérico producido por los sustituyentes voluminosos en *orto*, el responsable de la disminución de los rendimientos (por ejemplo, **5k,** 41 % y **5m**, 57 %).

3.1.3. Propuesta de mecanismo de ciclación de α-amidosulfonas acíclicas.

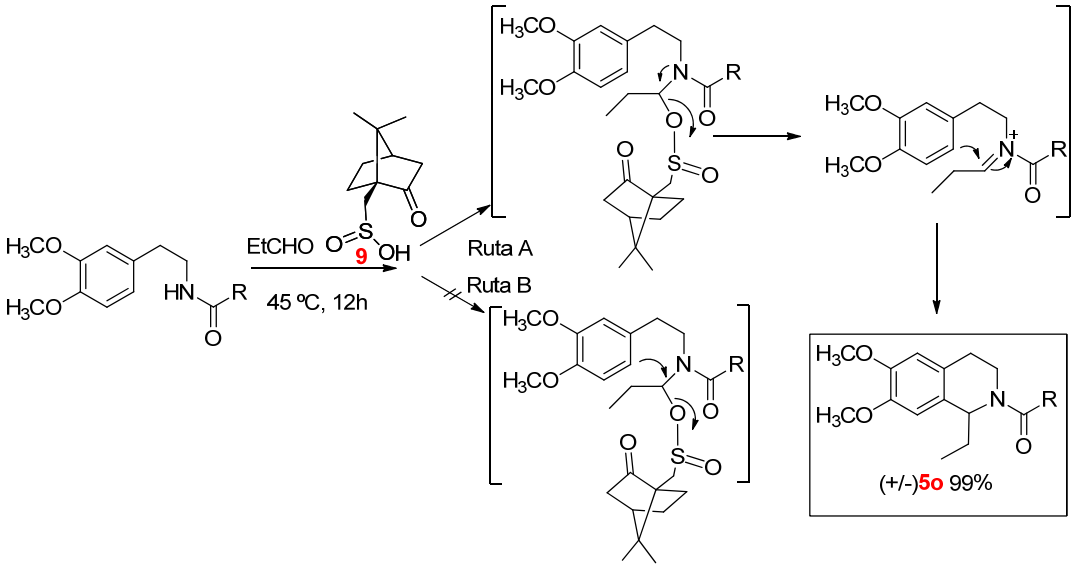
El mecanismo que proponemos para esta reacción pasa por un intermedio de tipo α-sulfonamida, basándonos en los intermedios aislados por Petrini *et. al.* para reacciones análogas. A partir de aquí podríamos proponer dos posibles rutas: una que pueda evolucionar a un intermedio de tipo aciliminio, más reactivo, capaz de ser atacado por el anillo aromático a través de un mecanismo de tipo S_N1 o bien, otra en la que el anillo aromático ataque directamente al Cα a la sulfona en un mecanismo de tipo S_N2 (esquema 3.7).



Esquema 3. 7

Para investigar estas posibilidades, se eligió realizar una prueba con el ácido (1*S*)-(+)-10-canfosulfínico (**9**) el cual, al presentar un estereocentro, nos permitiría comprobar si la naturaleza quiral de la sulfona afectaba al curso estereoquímico de la reacción[58], lo que nos haría inclinarnos por un mecanismo de tipo S_N2 (ruta b, esquema 3.7). El uso de auxiliares quirales en la síntesis asimétrica de THIQs ha sido ampliamente estudiado debido al gran número de alcaloides naturales que presentan quiralidad en la posición C1. Entre estas metodologías, cabe destacar el empleo de sulfóxidos quirales[59] y su posterior ciclación via Pictet Spengler como método sintético.

Aunque la ciclación tuvo lugar de forma cuantitativa, tampoco en este caso fue posible aislar el intermedio de α-amidosulfona. Sin embargo, la obtención de **5o** en forma racémica nos induce a pensar que el mecanismo del proceso implica un intermedio de tipo catión aciliminio que, al ser plano, puede ser atacado con igual probabilidad por ambas caras. Así, la sulfona actuaría como grupo saliente, desplazado por el par de electrones del nitrógeno (ruta a, esquema 3.8).

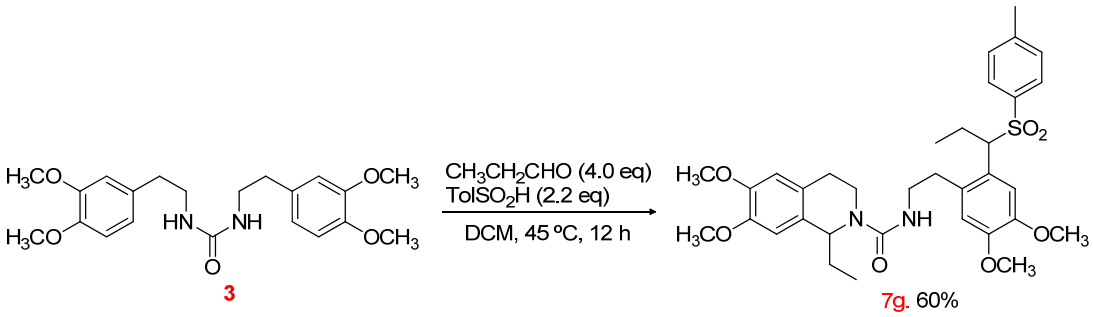


Esquema 3. 8

[58](a).Weygand, F.; Steglich, W. *Chem. Ber*. **1965**, *98*, 487.(b) Gizeki, P.; Youcef, R. A.; Poulard, C.; Dhal, R.; Dujardin, G. *Tetrahedron Lett*. **2004**, *45*, 9589.(c) Unterhalt, B.; Mohr, R. *Synthesis*, **1985**, 973.

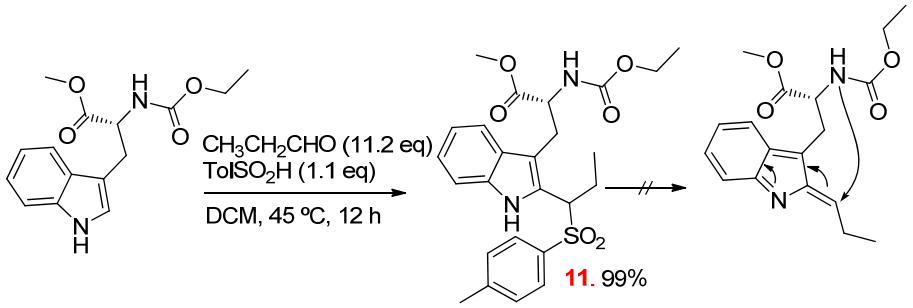
[59](a) Gremmen, C.; Wanner, M. J.; Koomen, G.-J. *Tetrahedron Lett*. **2001**, *42*, 8885.(b) Czarnocki, Z.; Mieczkowski, J. B.; Kiegiel, J.; Arazny, Z. *Tetrahedron:Asymmetry* **1995**, *6*, 2899.(c) Czarnocki, Z.; Arazny, Z. *Heterocycles* **1999**, *51*, 2871.

Por otro lado, en algunas reacciones, empleando las condiciones de ciclación indicadas, se han observado productos de reacción compatibles con la formación de las especies **I**. Así, en la reacción del derivado de urea **3** con el propanal se obtuvo el compuesto **7g**, en el que dicho intermedio **I** ha formado un enlace carbono-carbono con uno de los anillos aromáticos activado, posterior a la formación de una tetrahidroisoquinolina con el otro anillo aromático (esquema 3.9). Por otra parte, en la reacción entre el *N*-etoxicarboniltriptofanato de etilo y el propanal, en nuestras condiciones de reacción habituales, no se aisló el derivado de β-carbolina esperado, sino el compuesto **11**, lo que demuestra que en este caso la nucleofilia del nitrógeno se ve superada por la del anillo de indol, lo que lleva a la incorporación del intermedio **I** a la posición 2 de dicho heterociclo. Aunque el compuesto **11** podría considerarse un intermedio potencial en la formación de un derivado de tetrahidroisoquinolina a través de una eliminación de ácido toluenosulfínico seguida de una adición de Michael intramolecular, no observamos este proceso al aumentar la temperatura ni tras aplicar condiciones descritas en la biblografía[60] para compuestos muy similares, consistentes en tratamiento con fluoruro potásico y alúmina a temperatura ambiente (esquema 3.10).



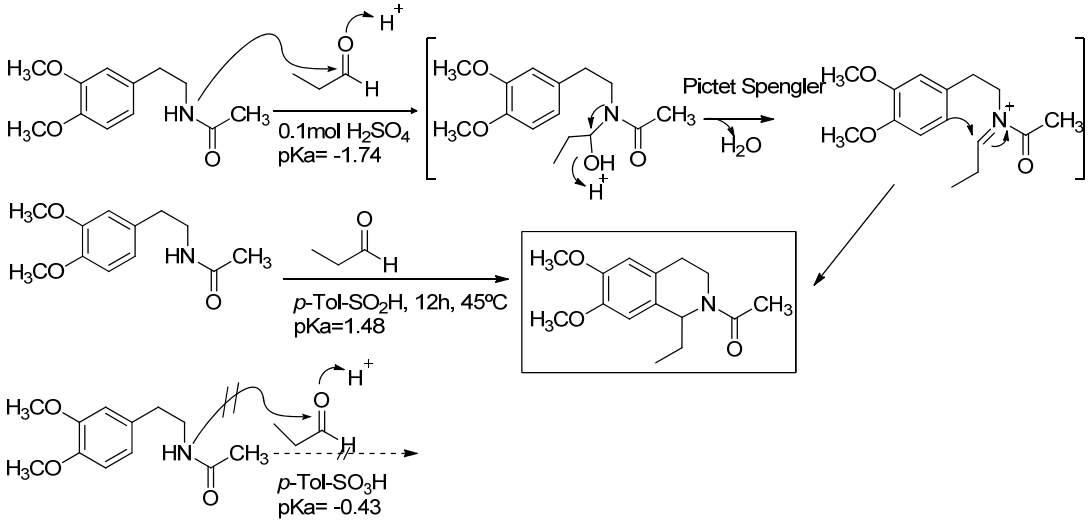
Esquema 3. 9

[60]Ballini, *R.*; *Palmieri, A.; Petrini*, *M.*; *Shaikh*, R.R. *Adv. Synth. Catal,* **2008,** *350,* 129.



Esquema 3. 10

Buscando aportar más datos que justificaran el mecanismo propuesto, realizamos un estudio orientado a descartar que el ácido sulfínico actuara en nuestras reacciones como un simple ácido de Brönsted que permitiera la reacción de Pictet-Spengler aumentando la electrofilia del aldehído por el mecanismo habitual. Se eligió como modelo un ácido muy fuerte como el sulfúrico, que cataliza las reacciones de ciclación a través del catión aciliminio por su elevada acidez (pKa = -1,74) y se comparó su reacción con la del ácido *para*-toluenosulfónico. Este último presenta una acidez menor que la del sulfúrico (pKa 0,43) y no es capaz de catalizar la ciclación, pero su acidez es mayor que el del ácido sulfínico (pKa = 1,48) que sí es capaz de ciclar la estructura, por lo que podemos afirmar que la reacción con el ácido sulfínico no transcurre mediante la protonación del aldehído si no que participa de forma activa en la reacción. Además se ha observado que es necesario al menos un equivalente de ácido sulfínico para que la reacción tenga lugar, mientras que el ácido sulfúrico promueve la reacción en cantidades catalíticas (esquema 3.11).

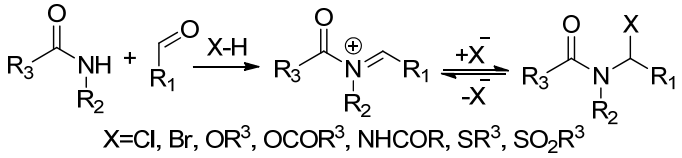


Esquema 3. 11

Ácido	pKa	Rdto.%
H_2SO_4/AcOH	-1.74/4.8	99
$TolSO_3H$	-0.43	-
$TolSO_2H$	1.48	99

Tabla 3. 2

La propuesta de los compuestos **I** como intermedios en la formación de α-amidosulfonas supone una diferencia respecto a la propuesta de Petrini[61], que plantea la formación de un intermedio aciliminio por reacción entre la amida y el aldehído, para posteriormente ser atacado por el ácido sulfínico, generándose así la α-amidosulfona (esquema 3.12).



Esquema 3. 12

3.1.4. Conclusiones.

Podemos concluir que hemos puesto a punto una reacción para la obtención de *N*-acil THIQs, en un solo paso y en condiciones de reacción suaves en cuanto a temperatura y acidez y que evita el empleo de ácidos fuertes de Brönsted o de Lewis, necesarios en los protocolos descritos hasta el momento.

Además, hemos proporcionado evidencias que apoyan un nuevo mecanismo en la generación de los sistemas de THIQ *vía* α-amidosulfonas.

[61] Petrini, M. *Chem. Rev*. **2005**, *105*, 11.

3.2. Aplicación de las α-amidosulfonas a la síntesis del núcleo de las saframicinas. Estrategia ACE-D-B.

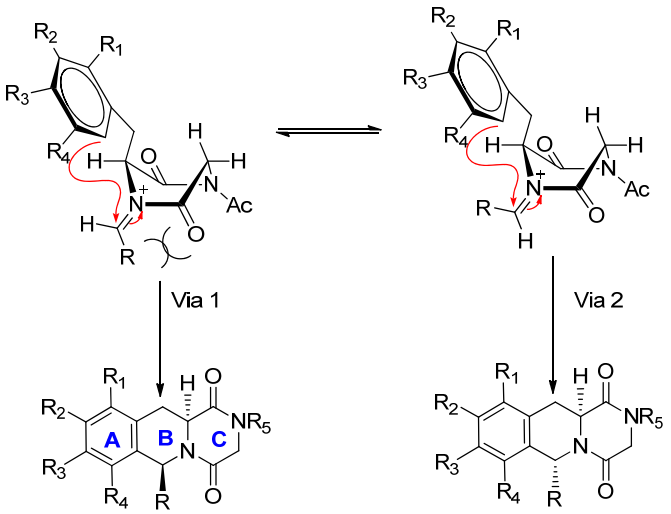
3.2.1. Ensayos sobre modelos simplificados. Síntesis del anillo AC-B.

3.2.1.1. Antecedentes.

El desarrollo de métodos que permitan alcanzar las estructuras requeridas minimizando el número de pasos de una síntesis y suavizando las condiciones descritas hasta el momento, es uno de los objetivos que abordan las nuevas metodologías sintéticas. En esta línea van encaminadas las últimas aportaciones a la obtención de análogos de saframicinas donde se han puesto a punto nuevas reacciones para la obtención del anillo B[62] disminuyendo el número de pasos de reacción[63] e incluso incorporando métodos biocatalíticos[64]. Para ello se han valido de modelos simplificados que permiten estudiar la viabilidad de estas reacciones propuestas.

En cuanto a la estereoquímica obtenida durante la síntesis de los sistemas de saframicinas, podemos apreciar diferentes disposiciones espaciales en la posición 6 dependiendo de los sustituyentes presentes en el intermedio de catión aciliminio que se genera durante la ciclación. Si éstos no suponen un gran impedimento, el intermedio formado seguirá la vía 1, mientras que si las interacciones entre el grupo R y el grupo carbonilo son elevadas, esta disposición se verá afectada, siendo más estable la formación del alqueno E en el fragmento aciliminio (vía 2, esquema 3.13). Así pues, hasta el momento, el estudio de la ciclación que genera el anillo B de modelos del fragmento ABC de la saframicina conduce a la disposición *trans* entre los hidrógenos de las posiciones C6-C11a, tanto en condiciones clásicas de Pictet- Spengler[65] como empleando una variante de la misma[66] y sólo se favorece el intermedio menos estable (*Z*), el de mayor impedimento en el intermedio que contiene el sustituyente benciloximetilo dando lugar a una disposición relativa *cis*[67] (vía 1).

[62] Ortín, I.; González, J. F.; de la Cuesta, E.; Avendaño, C. *Bioorg. Med. Chem.* **2010**, *18*, 6813.
[63] Yokoya, M.; Shinada-Fujino, K.; Saito, N. *Tetrahedron Lett.* **2011**, *52*, 2446.
[64] Koketsu, K; Minami, A.; Watanabe, K.; Oguri, H; Oikawa, H. *Curr. Opin. Chem. Biol.* **2012**, *16*, 142.
[65] Ong, C. W.; Lee, H. C. *Aust. J. Chem.* **1990**, *43*, 773.
[66] González, J. F.; de la Cuesta, E., Avendaño, C. .*Tetrahedron Lett.* **2003**, *44*, 4395.
[67] Ortín, I.; González, J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2009**, *65*, 2201.



Esquema 3. 13

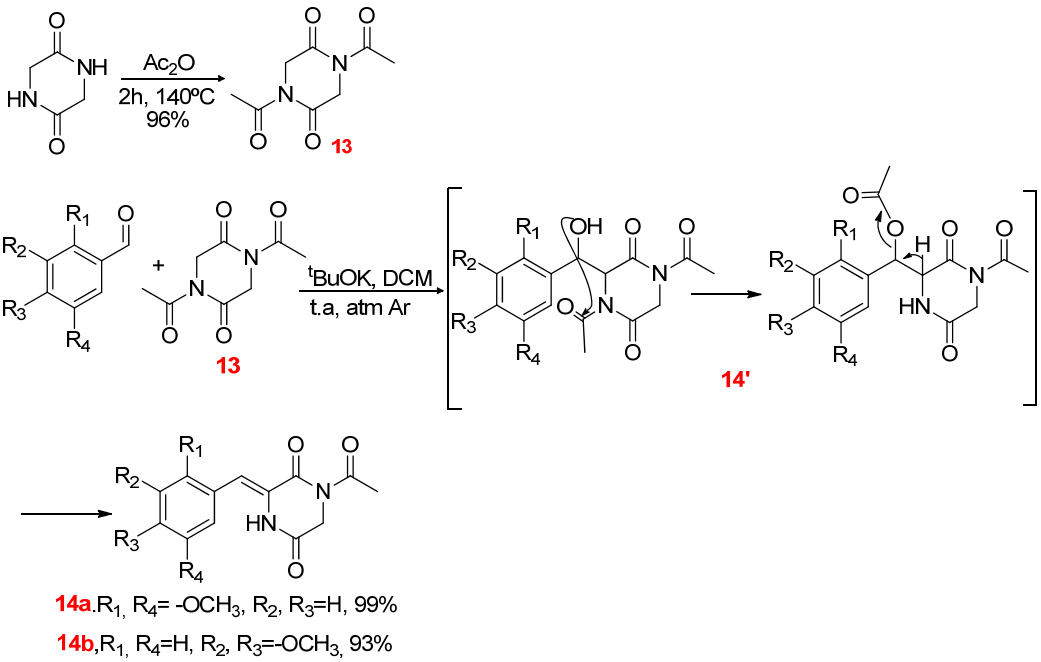
3.2.1.2. Reacciones de monocondensación.

En vista de la complejidad de las rutas sintéticas publicadas hasta el momento, nosotros proponemos una nueva metodología de síntesis mediante el empleo de α-amidosulfonas intentando generar los sistemas deseados con la esteroselectividad presente en los compuestos naturales. Los modelos sobre los se ensayaron estas reacciones pretenden la puesta a punto de la ciclación del anillo B, para más tarde aplicar esta ciclación sobre las estructuras que contienen los anillos ACED. Atendiendo así al gran problema de las síntesis totales de Saframicina A[68] y Saframicina B[69] que reside en la obtención del anillo B, el cual requiere la ruptura del enlace amida como vía para lograr una ciclación de Pictet Spengler, esquema 1.17 (compuesto **VIII**) y esquema 1.18 (compuesto **IV**).

En una primera aproximación a estructuras que contengan parte del núcleo de la saframicina, sobre las que poder realizar estudios de ciclación del anillo B, se prepararon los compuestos **14a** y **14b** (esquema 3.14) mediante una reacción de condensación aldólica entre los aldehídos comerciales 2,4- y 3,5-dimetoxibenzaldehído y la *N*,*N*-diacetil-1,4-piperazinadiona (**13**). Esta reacción nos proporciona un sistema de ciclos AC análogos a los de la estructura de las saframicinas.
La *N*,*N*-diacetil-1,4-piperazinadiona (**13**) se preparó a partir de la 1,4-piperazinadiona por calentamiento en anhídrido acético (esquema 3.14). La reacción de condensación requiere que la piperazina se encuentre acetilada ya que así se evita la interferencia de los grupos

[68]Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957.
[69]Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 3712.

NH ácidos y, además, los grupos acetilo favorecen dicha condensación por conferir una asistencia anquimérica[70] (intermedio **14'**, esquema 3.14).



Esquema 3. 14

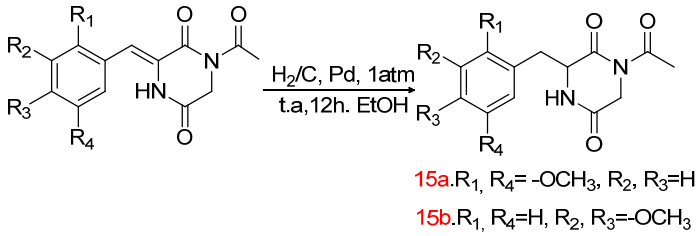
Todos los intentos de ciclación de los compuestos que presentan el doble enlace exocíclico empleando la metodología aplicada previamente por otros miembros de nuestro grupo de investigación,[71] basada en el uso de acetales y triflato de trimetilsililo como catalizador, habían resultado infructuosos, y también lo fueron todos los intentos realizados empleando nuestra metodología. Este fracaso se atribuyó a la rigidez debida a la hibridación sp^2, por lo que se procedió a la reducción de la insaturación según lo descrito en condiciones bibliográficas[72], para poder ensayar la ciclación del anillo B.

3.2.1.3. Reacción de reducción.

Esta reacción se realiza en condiciones suaves de hidrogenación catalítica proporcionándonos los compuestos **15a** y **15b** (esquema 3.15) que presentan una estructura

[70]Gallina, C.; Liberatori, A.; *Tetrahedron*. **1974**, *30*, 667.
[71]González J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2004**, *60*, 6319.
[72]Kanmera, T.; Lee, S.;Aoyagi, H.; Izumiya, N. *Tetrahedron* Lett. **1979**, *46*, 4483.

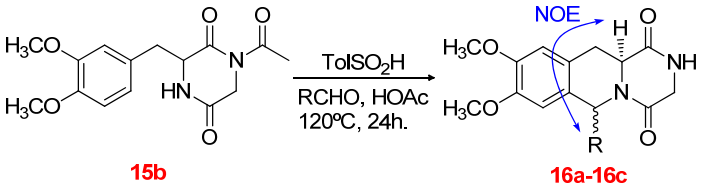
donde la dicetopiperazina adquiere una disposición de tipo bote que permite la total planaridad de los dos enlaces de amida[73].



Esquema 3. 15

3.2.1.4. Reacción de ciclación del anillo B en sistemas AC.

Las condiciones previamente establecidas para la obtención de tetrahidroisoquinolinas a partir de amidas y carbamatos a través de intermedios de α-amidosulfona (esquema 3.6) no resultaron adecuadas sobre estos nuevos sustratos, por lo que fue necesario un cambio tanto en el disolvente como en la temperatura de la reacción (esquema 3.16). La aplicación de las nuevas condiciones (ácido acético a 120 °C) lleva a los productos de ciclación deseados pero producen la hidrólisis del grupo acilo que deja la función amida desprotegida, lo que dificulta su reactividad, por la baja solubilidad del compuesto hidrolizado, y su purificación en cromatografía sobre gel de sílice debido a su alta polaridad.



Esquema 3. 16

Comparando la reacción de ciclación entre aldehídos de distinta naturaleza (tabla 3.3) podemos apreciar que los rendimientos más bajos se presentan en aldehídos aromáticos debido a una velocidad de reacción menor que posibilita la hidrólisis del grupo N-acetilo

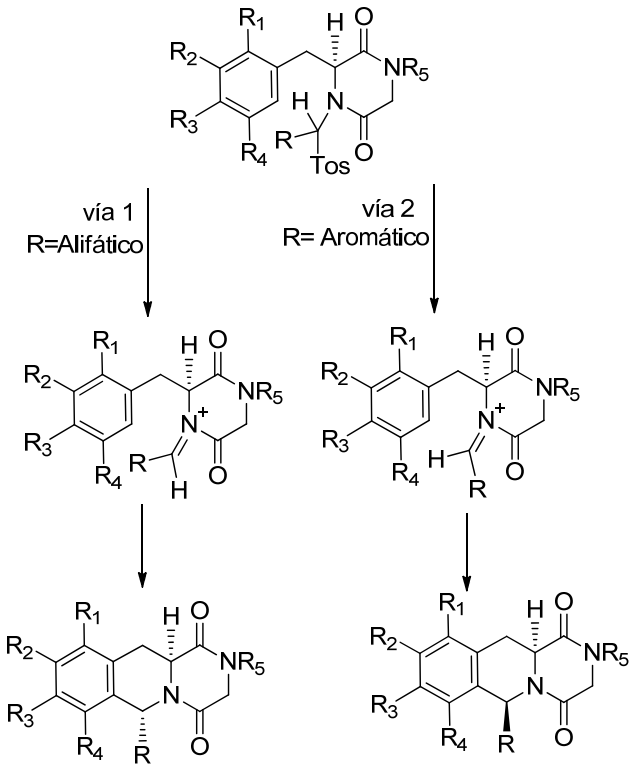
[73] Anteunis, M. J. O., *Bull. Soc. Chim. Belg.* **1978**, *87*, 8. (b) Sammes. G. P., *Progress Chem. Nat. Prod.*, **1975**, *32*, 51.

antes de la ciclación. En el caso de los aldehídos alifáticos la velocidad de ciclación es mayor, y ocurre antes de que se produzca la hidrólisis de la amida.

Compuesto	R-	Rdto.%
16a	C_2H_5-	62(22%**15b** hidrolizado)
16b	C_6H_5-	14(80%**15b** hidrolizado)
16c	*p*-BrC_6H_4-	11(85%**15b** hidrolizado)

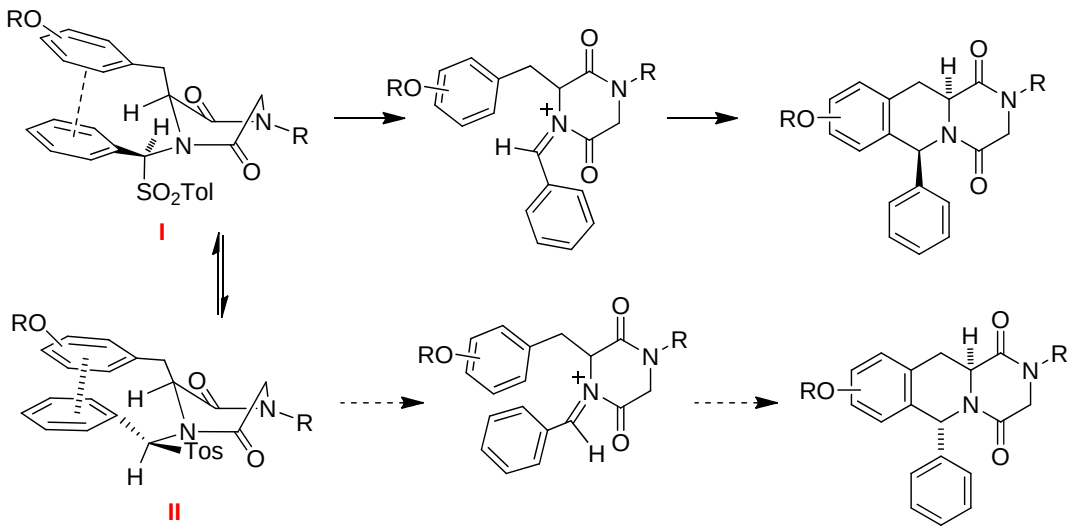
Tabla 3. 3

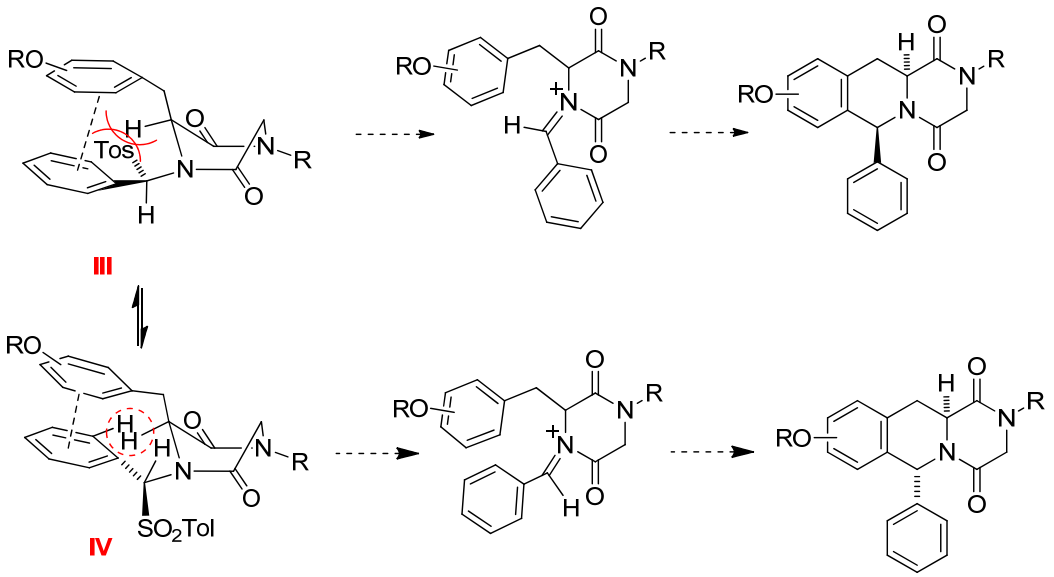
Si atendemos a la disposición de los hidrógenos H6 y H11 en estos compuestos, deducida a partir de los efectos NOE, podemos observar que aquellos derivados que poseen en R un sustituyente alifático, proporcionan una disposición *trans* (vía 1, esquema 3.17) mientras que los que poseen un anillo aromático, presentan una disposición *cis* (vía 2, esquema 3.17).



Esquema 3. 17

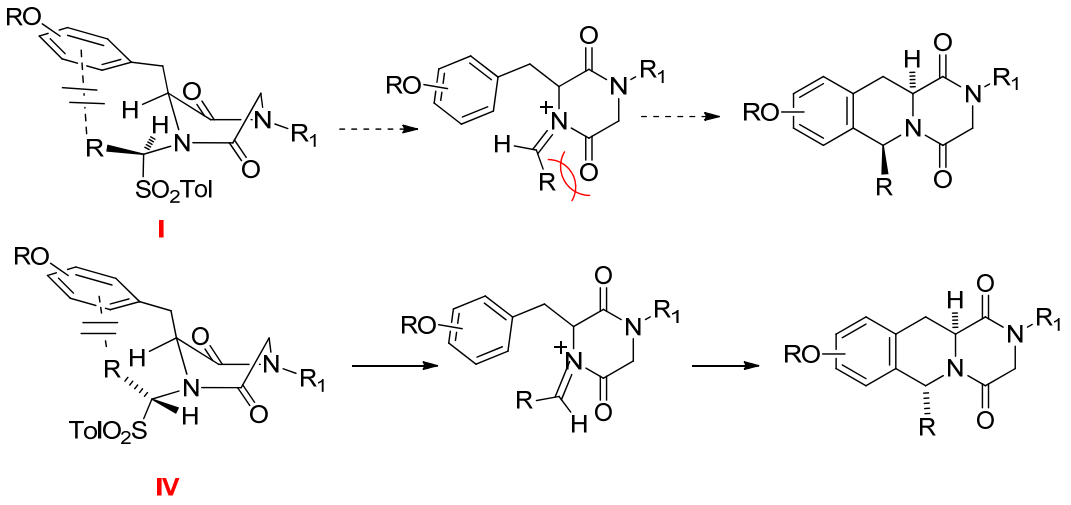
Para alcanzar los intermedios de catión iminio antes debemos pasar por un intermedio de α-amidosulfona que determinará la disposición relativa entre nuestros centros. En el caso de anillos aromáticos, independientemente del diasteroisómero de α-amidosulfona que se obtenga, siempre obtendremos el isómero *cis* debido a las interacciones de π-stacking entre el anillo A y el anillo aromático del aldehído (esquema 3.18). Así la conformación **I**, dirige a la formación del catión iminio *Z,* que es el que nos conduce al isómero *cis* (vía 2, esquema 3.17). De igual forma la disposición del intermedio **III** debería rendir el diastereoisómero *cis* pero debido al impedimento estérico que se genera entre el tosilo y el anillo A en el intento de disposición antiperiplanar resulta inviable la formación del catión iminio. Las conformaciones **II** y **IV** que conducirían a la disposición *trans* (vía 1, esquema 3.17) no alcanzan la disposición del catión iminio requerida para la ciclación. Tanto en el caso **II** como en el **IV** la interacción de π-stacking fija una disposición entre los anillos aromáticos que evita la eliminación del grupo tosilo, bien por no permitir la disposición antiperiplanar entre el grupo tosilo y el par de electrones del nitrógeno (**II**) o bien por el impedimento generado entre H3 y los protones del anillo aromático del aldehído (**IV**).
Puesto que **I** y **III** están en equilibrio con los materiales de partida y, por tanto, entre ellos, el único producto final observado es el compuesto tricíclico *cis*.





Esquema 3. 18

En compuestos con sustituyentes alifáticos (esquema 3.19), la naturaleza de R no permite el π-stacking que estabiliza el intermedio de α-amidosulfona en el intermedio **I** a la vez que estas interacciones tampoco fijan una disposición en el intermedio **IV**, que eviten la eliminación. Por lo tanto la disposición más estable en el intermedio de catión iminio, al no presentar un impedimento estérico entre el grupo carbonílico y el sustituyente alifático, es la que conduce al catión iminio *E* y por tanto al isómero *trans*.



Esquema 3. 19

De estos razonamientos se puede deducir, que las reacciones de ciclación a través de intermedios de α-amidosulfona permiten obtener de forma diastereoselectiva los sistemas ABC con la disposición presente en los anillos de saframicina, para los casos en que los aldehídos posean sustituyentes aromáticos. Esta metodología presenta la ventaja sobre la Pictet-Spengler convencional[74] y otras variantes de ella[75] de generar estereocentros con la configuración opuesta a la descrita en la bibliografía, y coincidente con la observada en los productos naturales.

3.2.2. Ensayos sobre estructuras simplificadas conteniendo los anillos ACE-B.

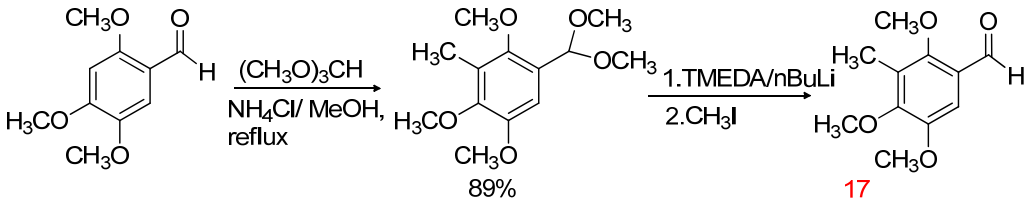
3.2.2.1. Introducción

Después de comprobar la posibilidad de realizar ciclaciones del anillo B en modelos simplificados de saframicinas mediante la formación de intermedios de α–amidosulfona (**16a – 16c**), nos planteamos aplicar dichas condiciones a estructuras más complejas y similares al núcleo de los compuestos naturales. Las dificultades ocasionadas por la hidrólisis del grupo N-acetilo que protege uno de los nitrógenos de 2,5-piperazinadiona en los sistemas AC podrían superarse si se partiese de sistemas ACE, no abordados en la bibliografía hasta el momento. Estos sistemas no presentan un enlace lábil de imida y poseen grupos aromáticos que favorecen su solubilidad, lo cual nos proporcionaría unas condiciones más favorables de reacción.

3.2.2.2. Síntesis del aldehído de partida

Para obtener los anillos aromáticos que contienen el núcleo de saframicina necesitábamos metilar la posición 3 del 2,3,5-trimetoxibenzaldehído comercial. Para ello, protegimos el aldehído en forma de acetal[76] y mediante una *o*-litiación asistida en presencia de TMEDA, que evita la formación de especies agregadas,[77] y posterior metilación por adición de yoduro de metilo[78] alcanzamos el compuesto **17** con un rendimiento global del 93%[79].

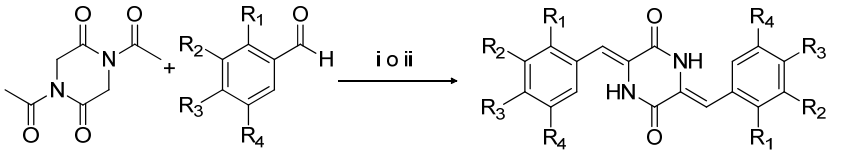
[74]Ong, C. W.; Lee, H. C. *Aust. J. Chem*. **1990**, *43*, 773.
[75](a)Gonzalez J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2005**, *61*, 7447. (b) González J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2004**, *60*, 6319.
[76]Azzena, J.; Denurra, T.; Melloni, G.; Piroddi, A. M. *Synthesis*, **1990**, 313.
[77]Gawley, R. E.; Aubé, J. Principles of Asymmetric Synthesis. Tetrahedron Organic Chemistry Series, Vol. 14. Pergamon Press, **1996,** 77.
[78]a) Danishefsky, S. J.; Berman, E.; Cvetovich, R.; Minamikawa, J. *Tetrahedron Lett.* **1980**, *21*, 4819. b) Winkle, M. R.; Ronald, R. C. *J. Org. Chem*. **1982**, *47*, 2101.
[79]González J. F.; de la Cuesta, E.; Avendaño, C. *Synth. Commun.* **2004**, *34*, 1589.



Esquema 3. 20

3.2.2.3. Reacción de dicondensación.

La condensación aldólica entre la 2,5-diacetil-1,4-piperazinadiona y dos equivalentes de aldehídos aromáticos en medio básico, dio lugar a los compuestos de dicondensación con buenos rendimientos. Para lograr la doble condensación, fue necesario forzar las condiciones de reacción con respecto a las expuestas en la monocondensación, observándose además una relación entre las condiciones y el tipo de sustitución de los anillos aromáticos. Las condiciones empleadas para la obtención de los compuestos **18a** y **18b** (esquema 3.21), reflujo en DMF y trietilamina como medio básico,[80] son insuficientes cuando se emplea el aldehído **17**, que presenta un grupo carbonilo menos electrófilo y con mayor impedimento estérico. Las condiciones básicas de Cs_2CO_3 usando una mezcla de AcOEt/DMSO como disolvente que han sido puestas a punto en este trabajo para la obtención del compuesto **19** ofrecen una ventaja apreciable en el rendimiento de dicha condensación en comparación con la descrita en bibliografía, al introducir como medio de reacción una mezcla 5:1 de acetato de etilo y dimetil sulfóxido, alcanzando un rendimiento del 86% frente al 64 % descrito en la bibliografía [81].



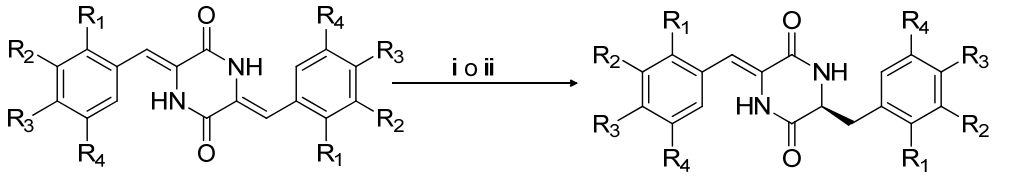
Esquema 3. 21

[80] Gallina, C; Richardson, L.; Welch, C.; Calvert, S. *J. Am. Chem. Soc.* **1929**, *51*, 3074.
[81] Shawe, T. T.; Liebeskind, L. S. *Tetrahedron* **1991**, *47*, 5643.

La construcción de estas estructuras simétricas nos proporciona los anillos ACE de una forma rápida, lo que permite potencialmente plantear una ruta muy breve al núcleo de las saframicinas si se logra diferenciar los dos grupos arilmetileno para poder emprender vías diferenciadas en la obtención de los anillos B y D.

3.2.2.4. Reducción selectiva del doble enlace exocíclico.

La necesidad de romper la simetría de los sustituyentes becilideno en las posiciones C3 y C6 de la piperazinadiona nos plantea la búsqueda de una reacción que afecte selectivamente a uno de los dos. Optamos por la reducción de uno de los dos dobles enlaces en presencia de zinc en ácido acético[82] como método de diferenciación, la cual genera los correspondientes derivados de 3-bencil-6-bencilidenpiperazina-2,5-diona (esquema 3.22).



i.Zn/HOAc,125ºC, 20h ii.Zn/HOAc,140ºC, 48h

i.20a. R_2,R_3=-OCH_3, R_1, R_4= H. 80%
i.20b. R_2,R_3= H, R_1, R_4= -OCH_3. 83%
ii.20c. R_1,R_3, R_4=-OCH_3, R_2= CH_3. 39%

Esquema 3. 22

Esta reducción selectiva de un doble enlace se debe a la disposición que adopta el anillo aromático reducido tras producirse la hidrogenación del doble enlace, la libertad conformacional de este anillo le permite colocarse sobre el par de electrones π de la insaturación, en una conformación estabilizada mediante interacciones de π–stacking[83] (figura 3.1) que impiden estéricamente la reducción por una de las caras. Por otro lado, la deficiencia de carga creada por las interacciones de π–stacking evita la reducción por la cara opuesta, generándose los compuestos monorreducidos deseados.

[82] Marcuccio, S. M.; Elix, J. A. *Aust. J. Chem.* **1984**, *37*, 1791.
[83] Bloom, J.W.C.; Wheeler, S.E. *Angew. Chem., Int. Ed.*, **2011**, *50*, 7847.

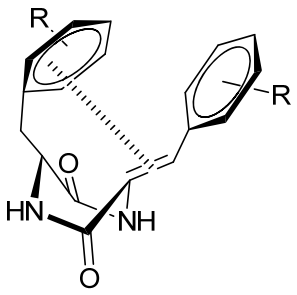
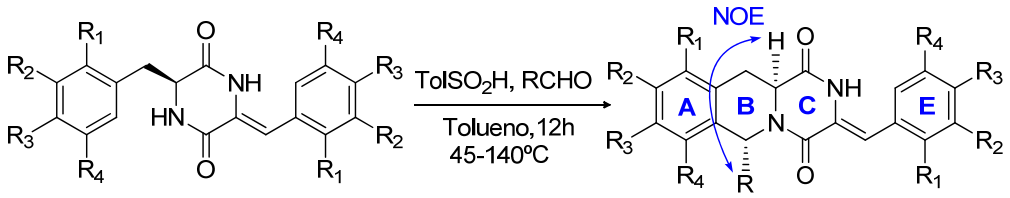


Figura 3. 1

El bajo rendimiento obtenido del compuesto totalmente sustituido **20c** (39 %) es atribuido a su difícil extracción del medio de reacción debido a su retención de este en las sales de zinc generadas en el proceso.

3.2.2.5. Reacción de ciclación del anillo B en sistemas ACE.

La mayor planaridad de las estructuras del tipo 3-bencil-6-bencilidenpiperazina-2,5-diona con respecto a sus análogos derivados de pirazinoisoquinolina (**16a**, **16b**) a causa de la presencia del doble enlace exocíclico favorece la reacción vía α-amidosulfona, conduciendo a una más fácil ciclación del anillo B (esquema 3.23). Estudiando los resultados obtenidos en la tabla 3.4 para esta reacción, observamos que a medida que aumenta el impedimento estérico del anillo A, que desempeña el papel de nucleófilo, se hace necesario un incremento de temperatura para lograr la ciclación.
De igual forma se ha observado que al incrementar la electrofilia de los aldehídos aromáticos con sustituyentes electroatractores, en contra de lo que cabría esperar, no mejoran los rendimientos de la reacción de ciclación, sino que de hecho disminuyen ligeramente. Podemos concluir, por tanto, que los factores estéricos tienen un papel más importante que los electrónicos en el curso de la reacción, especialmente si los sustituyentes están en *orto*, y esto se pone de manifiesto tanto si el impedimento estérico es aportado por el aldehído (**21c**, **21f**), como por el anillo aromático (**21e**,**21n** y **21r**). Por otro lado, a pesar de la mayor reactividad de los aldehídos alifáticos, proporcionan rendimientos moderados cuando se requiere el empleo de temperaturas elevadas, debido a que se evaporan durante la reacción a causa de su bajo punto de ebullición.

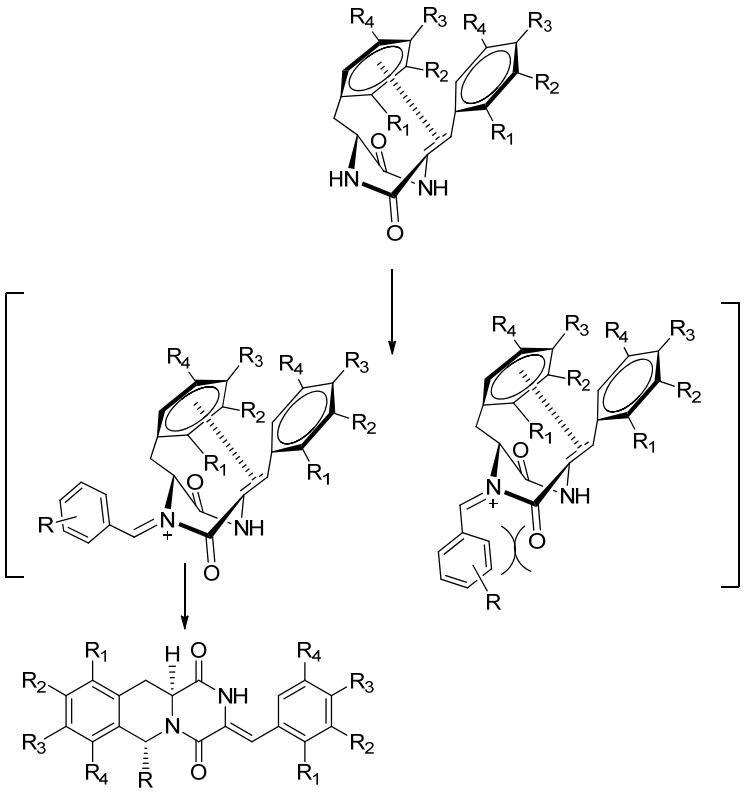


Esquema 3. 23

	Compuesto	R	T ºC	Rdto. %
R_2, R_3=OCH_3, R_1,R_4= H	21a	C_2H_5-	45	99
	21b	C_3H_7-	45	84
	21c	C_6H_5-	120	94
	21d	*p*-Br-C_6H_4-	120	83
	21e	*m*-$NO_2C_6H_4$-	120	81
	21f	*o*-$NO_2C_6H_4$-	120	80
	21g	*o*-Cl-C_6H_4-	120	87
R_1, R_4= OCH_3, R_2,R_3= H*	21h	C_2H_5-	120	27
	21i	C_6H_5-	135	85
	21j	C_6H_5CHCH-	135	82
	21k	*o*-Cl-C_6H_4-	135	80
	21m	*p*-Br-C_6H_4-	135	83
	21n	*m*-$NO_2C_6H_4$-	135	68
R_1, R_4, R_3=OCH_3, R_2= CH_3	21o	C_2H_5-	140	20
	21p	C_6H_5-	140	83
	21q	*p*-Br-C_6H_4-	140	85
	21r	*m*-NO_2-C_6H_4-	140	51

Tabla 3. 4

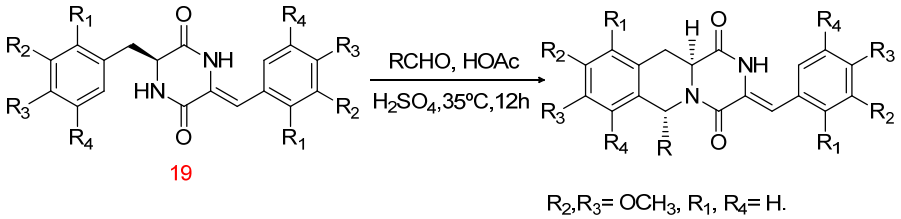
Fijándonos ahora en la estereoquímica de los productos, establecida mediante los efectos NOE encontrados, observamos que la disposición relativa que guardan los hidrógenos de las posiciones C6-C11a es *trans*, independientemente de si partimos de aldehídos aromáticos o alifáticos. Este hecho no se correlaciona con los datos encontrados en la ciclación ABC resumida en los esquemas 3.17 y 3.18. La explicación reside en la nueva disposición de esta estructura (esquema 3.24). En función de ella, el intermedio de α-amidosulfona formado no genera interacciones con el anillo A debido al π-stacking ya existente con los electrones π del sustituyente bencilideno. Por tanto, de acuerdo con los intermedios del esquema 3.17 (vía 1) el impedimento estérico entre el sustituyente R y el carbonilo de la dicetopiperazina dirige la disposición del intermedio aciliminio a la estereoquímica *trans.*



Esquema 3. 24

Una vez lograda la ciclación del anillo B del núcleo de las saframicinas, mediante nuestro método, y comprobando que la estereoquímica que nos ofrece la reacción es la opuesta a la

requerida, nos propusimos aplicar condiciones clásicas de Pictet-Spengler. Nuestro método consistió en el empleo de aldehídos en ácido acético como disolvente y en presencia de ácido sulfúrico como catalizador. Las diferencias obtenidas con respecto al empleo de ácidos sulfínicos no son significativas en cuanto a rendimientos y tampoco se consiguió obtener la configuración relativa presente en los productos naturales. La principal ventaja de este método es que permite emplear temperaturas más suaves (35ºC).[84]



Esquema 3. 25

	Compuesto	R	T ºC	Rdto. %
R_2, R_3=-OCH_3 ,R_1,R_4=H	21a	C_2H_5-	35	97
	21c	C_6H_5-	35	68

Tabla 3. 5

Nuestros estudios han conducido a una preparación de una serie de derivados funcionalizados del fragmento ABC de las saframicinas (compuestos **21**) mejorada en cuanto a rendimiento, generalidad y estereoselectividad respecto a lo descrito en la bibliografía.[85] No obstante, decidimos aplicar nuestras condiciones de ciclación a esqueletos que contuvieran otro tipo de sustituyentes distintos al bencilideno en la posición 6 de la piperazina, con objeto de tratar de conseguir la estereoquímica de los compuestos naturales. Decidimos para ello partir de un compuesto que poseyera el sistema de anillos ACED.

[84] En nuestro grupo se había llevado a cabo previamente la reacción entre el compuesto **20b** y el acetaldehído en una mezcla 4:1 de ácido acético y ácido trifluoroacético a 90 °C. López Cobeñas, A. Tesis Doctoral, p. 123. Universidad Complutense, 2008.

[85] González, J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron Lett*. **2003**, *59*, 8245.

3.2.3. Metodología de síntesis sobre el esqueleto ACE-D-B.

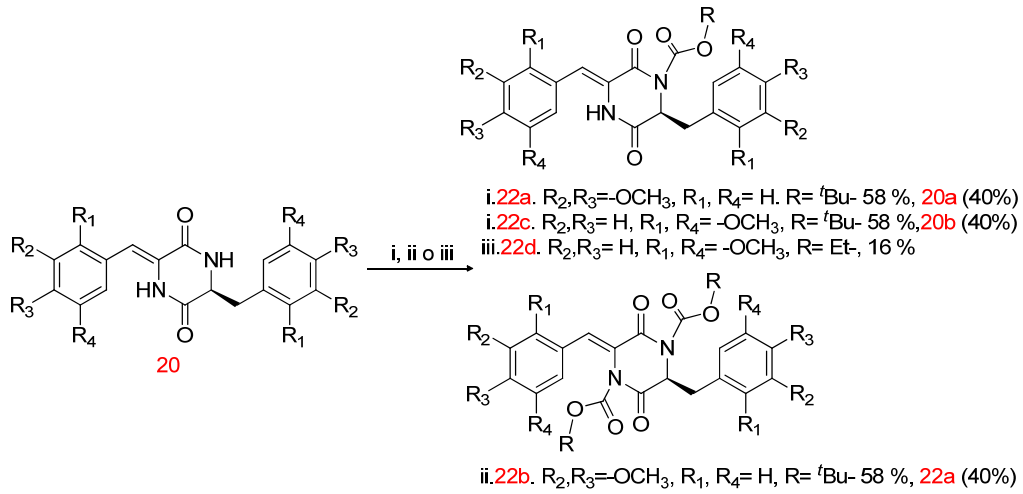
3.2.3.1. Introducción.

La estrategia sintética dirigida a la preparación de los anillos ACED, antes de abordar la ciclación del anillo B, ya ha sido estudiada por otros grupos de investigación, tanto para los esqueletos de las saframicinas[86] como de las renieramicinas,[87] lo que nos proporciona un conocimiento adicional sobre la viabilidad de esta ruta.
La ciclación del anillo D engloba una serie de reacciones en las que debemos incrementar la electrofilia del carbonilo en C1, para generar un intermedio de catión iminio, a través de un hemiaminal, que sea atacado por el anillo aromático del ciclo E.

3.2.3.2. Reacciones de activación de C1.

Una vez rota la simetría de la molécula con la reducción selectiva de uno de los dobles enlaces, aprovechamos esta diferenciación para introducir un grupo que debilite el enlace amida del C1 de la dicetopiperazina, y permita así la accesibilidad de nucleófilos de manera selectiva a uno de los dos carbonilos contenidos en la estructura. Así, mediante el empleo de anhídridos de alcoxicarbonilo o cloroformiatos de alquilo se pueden generar los carbamatos deseados en uno de los nitrógeno menos impedido de la piperazina (esquema 3.26).

[86] a. Kubo, A.; Saito, N.; Nakamura, M.; Ogata, K.; Sakai, S. *Heterocycles* **1987**,*26,* 1765. b. Kubo, A.; Saito, N.; Yamato, H.; Yamauchi, R.; Hiruma, K.; Inoue, S. *Chem. Pharm. Bull.* **1988**, *36*, 2607. c. Kubo, A.; Saito, N.; Yamato, H.; Masubuchi, K.; Nakamura, M. *J. Org. Chem.* **1988**, *53*, 4295.
[87] a. Yokoya, M.; Shinada-Fujino, K.; Yoshida, S.; Mimura, M.; Takada, H.; Saito, N.; *Tetrahedron* **2012**, *68* ,4166. b. Yokoya, M.; Shinada-Fujino, K.; Saito, N.; *Tetrahedron Letters*, **2011**, *52*, 2446.



Esquema 3. 26

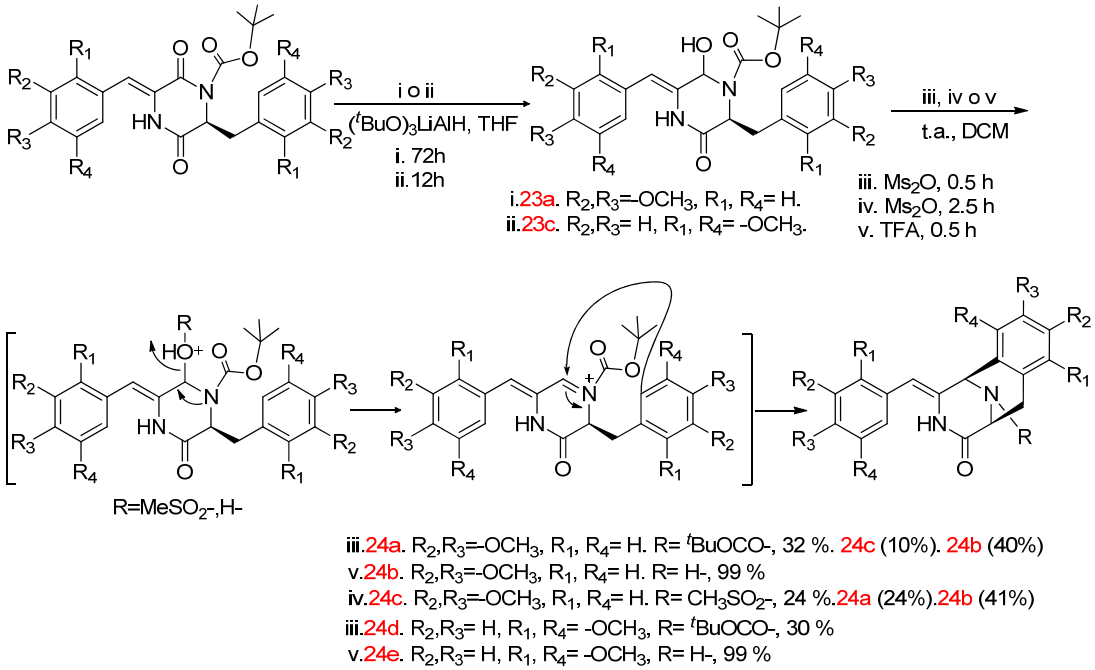
La formación de los monocarbamatos en el N2 (**22a**, **22b**, **22c**) compite con la formación del compuesto diacilado en las posiciones N2 y N5 (**22b**), a pesar de la diferenciación química generada en la estructura.[88] Por ello se hace indispensable sacrificar el rendimiento de la reacción para conseguir la selectividad requerida.

3.2.3.3. Obtención del anillo D.

Los compuestos monoacilados fueron sometidos a una reducción parcial del carbonilo C1 con un donador de hidruros impedido, que favorece la reducción selectiva de esta posición dando lugar a los compuestos **23**. La inestabilidad de estas estructuras[89] nos obligó a llevar a cabo inmediatamente la siguiente reacción, en la que se logra la formación del anillo D. Los dos métodos descritos en la bibliografía en estructuras similares para la activación de los hemiaminales **23**, se basan en su tratamiento con ácido fórmico (rendimientos entre 75[90]-89%[91]) o con anhídrido de mesilo. Tuvimos que descartar este último método porque conducía al compuesto **24a** con bajo rendimiento (32%) junto con el compuesto N

[88] Estos compuestos eran conocidos: López Cobeñas, A. Tesis Doctoral, pp. 91-93. Universidad Complutense, 2008.
[89] DeNinno M. P.*; Eller C.; and Etienne J. B. *J. Org. Chem.* **2001,** *66,* 6988.
[90] Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am.Chem. Soc.* **1990**, *112*, 3712.
[91] Tatsukawa, M.; Punzalan, L. C.; Magpantay H.D.; Villaseñor, I.M.; Concepcion, G. P.; Suwanborirux, K.; Yokoya M.; Saito N. *Tetrahedron* **2012**, *68,* 4166.

desprotegido y **24c**, que presenta un grupo mesilo en el nitrógeno del puente. El ácido fórmico nos condujo a los productos de ciclación **24b** y **24e** con buen rendimiento (90%), y experimentos posteriores empleando ácido trifluoroacético nos permitieron obtener rendimientos cuantitativos en esta reacción (esquema 3.27).



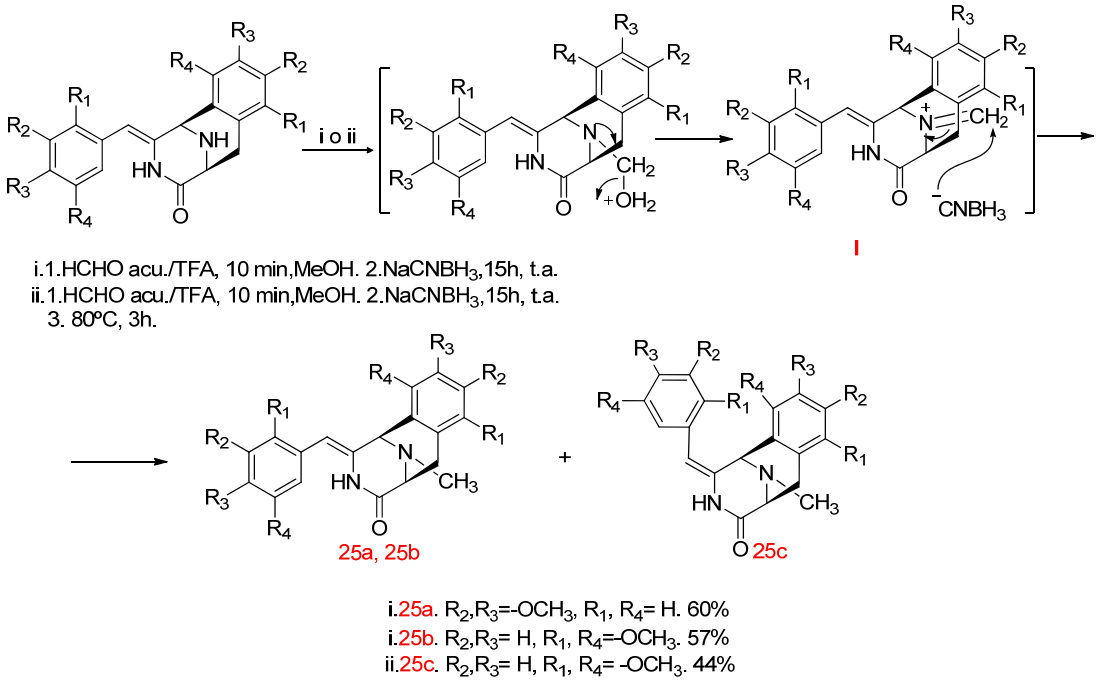
Esquema 3. 27

3.2.3.4. Reacción de metilación del nitrógeno puente.

La familia de las saframicinas posee un grupo metilo en el nitrógeno de amina situado en el puente común a los anillos C y D, por ello decidimos poner a punto la metilación de este nitrógeno sobre nuestras estructuras por alquilación reductora con formaldehído al 36% en presencia de ácido trifluoroacético, a través de la formación de un intermedio iminio seguida de reducción con cianoborohidruro sódico, un donador de hidruros estable en medio ácido (esquema 3.28).

En un intento de mejorar los rendimientos se incrementó la temperatura de la reacción, pero en esta condiciones se producía la isomerización del doble enlace

exocíclico. Este hecho también ha sido ya descrito por otros autores[92] pero no es relevante en nuestra ruta ya que el siguiente paso conlleva la reducción del doble enlace.



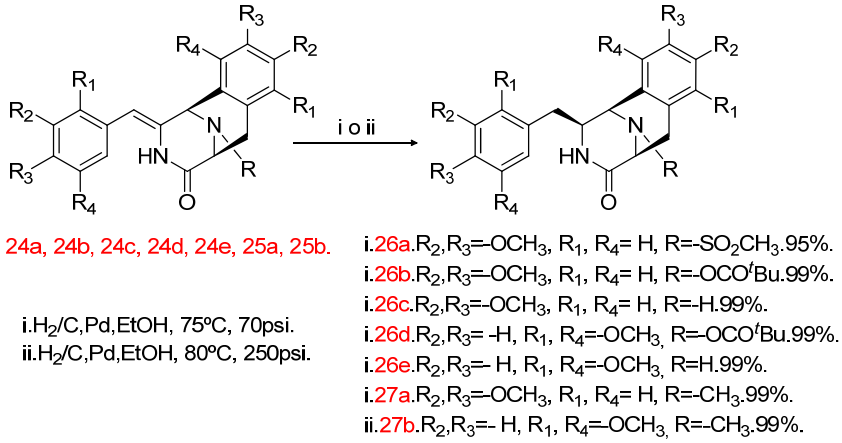
Esquema 3. 28

3.2.3.5. Reducción de la insaturación exocíclica.

La reducción del doble enlace exocíclico de compuestos correspondientes al fragmento ACDE de las saframicinas requiere algunas veces condiciones muy drásticas, con presiones de hidrógeno de hasta 1500 psi.[93] En nuestro caso, la mayor o menor facilidad de reducción de este doble enlace depende en parte de la posición de los sustituyentes del grupo bencilideno, ya que la reducción requiere un incremento de la presión cuando la sustitución de los grupos metoxi del anillo A se da en R_1 y R_4, como se observa comparando los casos **27a** (R_2, R_3 = OCH_3) y **27b** (R_1, R_4 = OCH_3) (esquema 3.29).[94]

[92] Tatsukawa, M.; Punzalan, L.C.; Magpantay H.D.; Villaseñor, I.M.; Concepcion, G. P.; Suwanborirux, K.; Yokoya M.; Saito N. *Tetrahedron* **2012**, *68,* 4166.
[93] Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am.Chem.Soc.* **1990**, *112*, 3712.
[94] Yokoya, M.; Shinada-Fujino, K.; Saito, N. *Tetrahedron Lett.* **2011**, *52*, 2446.

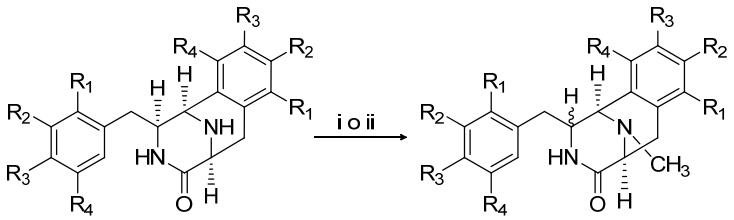
En vista de la elevada presión necesario para la reducción del doble enlace exocíclico del compuesto **25b** (250 psi), se optó por llevar a cabo en primer lugar la reacción de reducción y posteriormente practicar la metilación del nitrógeno. Esta decisión se basó en un antecedente bibliográfico en sustratos relacionados que sugería que la presencia de sustituyentes voluminosos en el nitrógeno puente dificulta la reducción del doble enlace exocíclico.[95] Efectivamente, el compuesto **24e** (análogo N-desmetilado de **25b**) pudo reducirse a 70 psi, proporcionando **26e**.



Esquema 3. 29

Una vez obtenidos los compuestos **26c** y **26e**, se metilaron en las condiciones expuestas en el punto 3.2.3.4 en las que se emplea cianoborohidruro sódico como donador de hidruros en medio ácido. Sin embargo, durante esta reacción se observó la epimerización del estereocentro en C2 (esquema 3.30).

[95] Kubo, A.; Saito, N.; Yamato, H.; Masubuchi, K.; Nakamura, M.*J. Org. Chem.* **1988**, *53*, 4295.

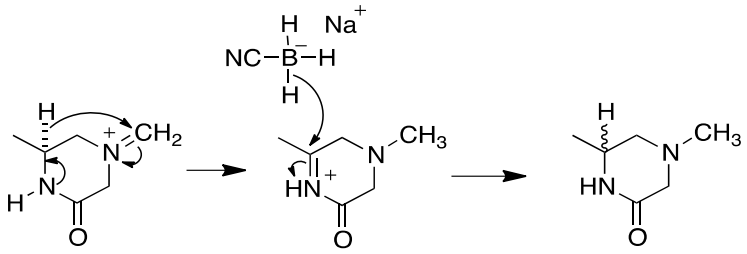


i.1.HCHO/TFA, 10 min, MeOH, 2.$NaCNBH_3$,15h, t.a
ii.1.HCHO/TFA, 10 min, MeOH, 2.$NaCNBH_3$,64h, t.a

i.27a.R_2,R_3=$-OCH_3$, R_1, R_4= H, *cis* 40%.(*trans* 58%)
ii.28a.R_2,R_3=$-OCH_3$, R_1, R_4= H, *trans* 58%.(*cis* 37%)
i.28b.R_2,R_3= H, R_1, R_4=$-OCH_3$, *trans* 53%
i.27b.R_2,R_3= H, R_1, R_4=$-OCH_3$, *cis* 23%

Esquema 3. 30

El mecanismo que proponemos para esta epimerización comienza con la formación del catión iminio representado en el esquema 3.31, seguida de una reacción azeno de Alder donde se transfiere un hidruro alílico de forma intramolecular y la reducción final del catión iminio resultante por el reactivo donador de hidruro (esquema 3.31).

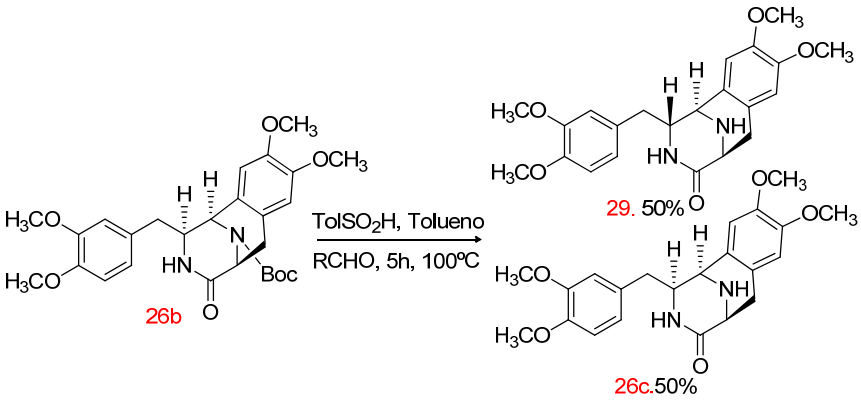


Esquema 3. 31

Debido a esta reacción de epimerización, no fue posible emplear la estrategia basada en llevar a cabo la metilación como última etapa.

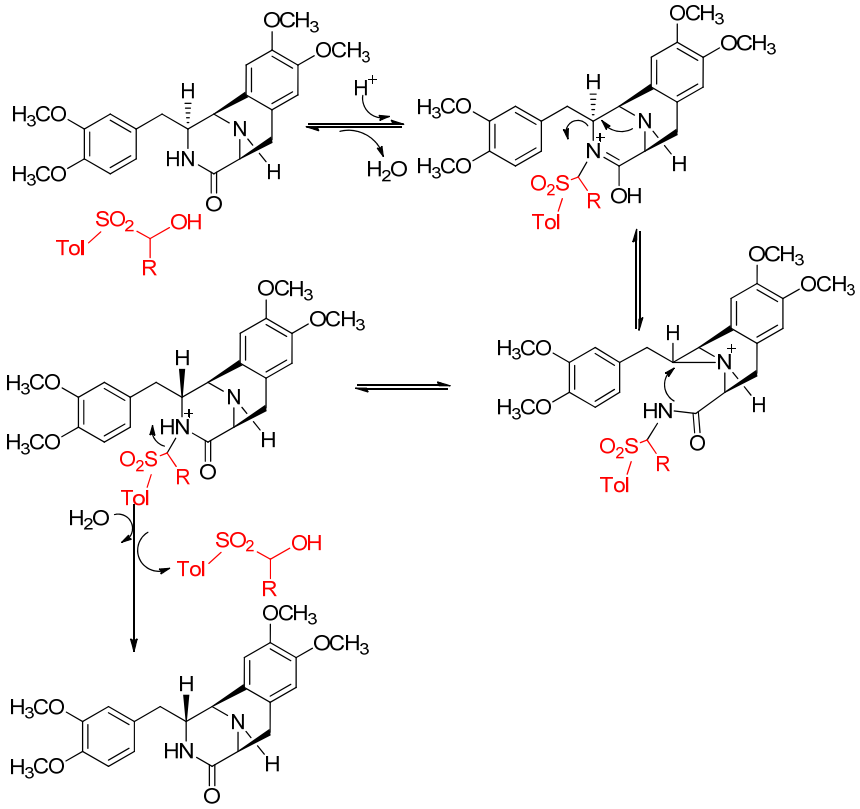
3.2.3.6. Reacción de ciclación del anillo B.

En los primeros intentos de formación del anillo B sobre las estructuras preparadas, se aplicaron las condiciones ya ensayadas para los sistemas ACEB (apartado 3.2.2.5), que consistían en tratamiento con ácido *p*-toluenosulfónico y el aldehído correspondiente a 100 ºC. Estas condiciones, aplicadas al compuesto **26b**, conducen a la hidrólisis del enlace carbamato seguida de la epimerización del centro C2, sin que se observen trazas del producto de ciclación.



Esquema 3. 32

El mecanismo propuesto para la epimerización del compuesto **26b** se encuentra recogido en el esquema 3.33.

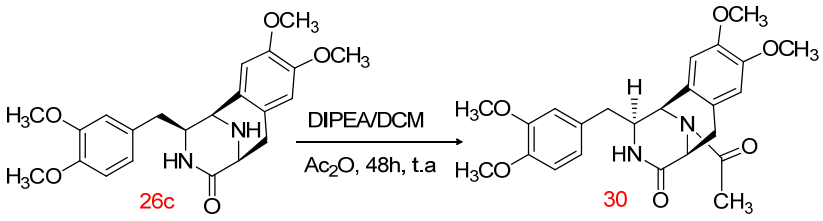


Esquema 3. 33

El grupo *terc*-butiloxicarbonil es lábil y fácil de perder en las condiciones de la reacción de ciclación y deja un hidrógeno sobre la amina. Una vez hidrolizado, se podría proponer un

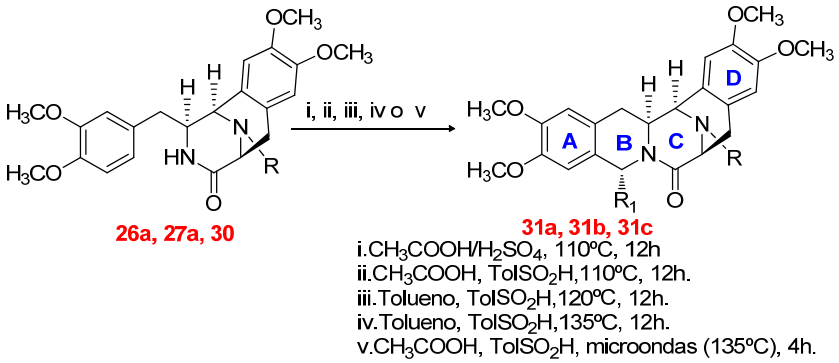
ataque del nitrógeno libre de la amina a la posición vecina que conduce a su ciclación sobre la posición 2 que abre el anillo de piperazina. Este ataque no sería posible para aquellos compuestos en los que hay sustituyentes aceptores de electrones (CH_3CO, CH_3SO_2) sobre el nitrógeno.

Para evitar el problema de la desprotección del grupo BOC, se decidió llevar a cabo un nuevo intento de ciclación del anillo B en un sustrato N-acetilado, que se preparó por tratamiento de **26c** con anhídrido acético en presencia de la base de Hünig, a temperatura ambiente (esquema 3.34):



Esquema 3. 34

Se estudió la ciclación del compuesto **30** (acetilado) y de los otros derivados (**26b, 27a**) que teníamos previamente sintetizados con sustituyentes alquilos y metanosulfonilo sobre el nitrógeno del puente, consiguiéndose los correspondientes productos de ciclación con un rendimiento bajo, pero sin que se observase epimerización en la posición 2.



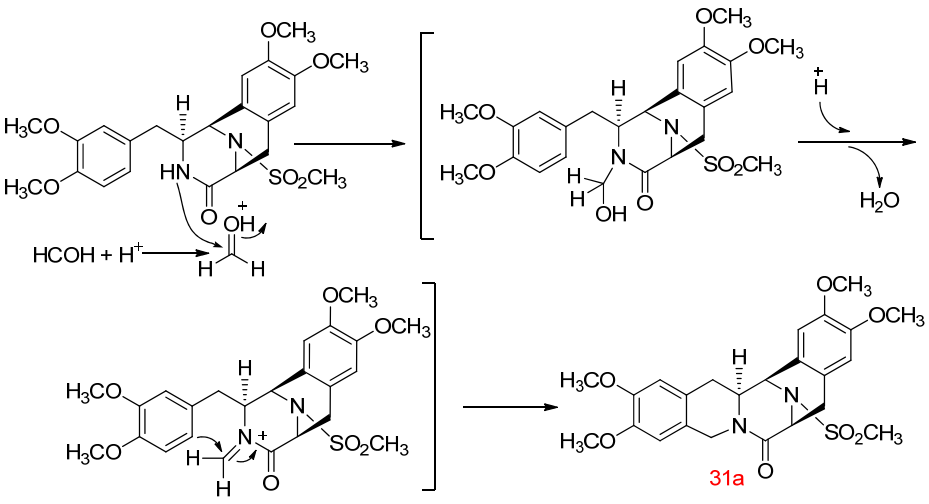
Esquema 3. 35

Comp. partida	Condiciones	R	R_1	Rdto%
26a	i	CH_3SO_2-	H-	14 (**31a**)
26a	ii	CH_3SO_2-	H-	23 (**31a**)
26a	i,ii,iii,iv	CH_3SO_2-	Ph	---[#]
27a	iii*	CH_3-	Ph-	20 (**31b**)**
27a	i	CH_3-	Ph-	8 (**31b**)
27a	iv	CH_3-	Ph-	8 (**31b**)
27a	v	CH_3-	Ph-	20 (**31b**)
27a	iii*	CH_3-	*p*-BrC_6H_4-	23 (**31c**)**
30	i,ii,iii,iv	$COCH_3$	Ph	----[#]

*Varios ensayos a diferentes temperaturas. A temperaturas > 135°C, el producto de partida se descompone.**La esterioquimica de los compuectos 31b y 31c fue obtenida por compración con los compuestos recogidos en la tesis doctoral de López Cobeñas, A., pp. 159-161. Universidad Complutense, 2008.[#] Se recupera el producto de partida.

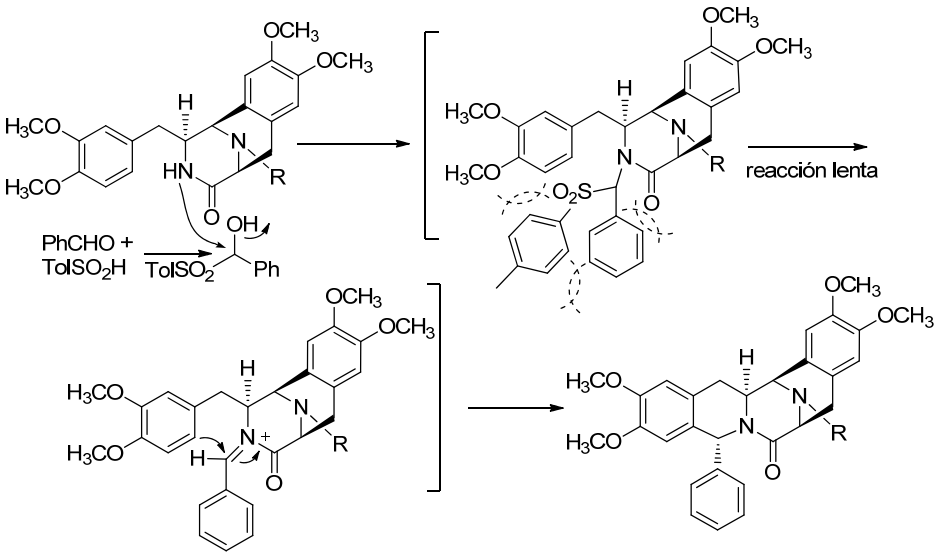
Tabla 3. 6

Aprovechando la mayor reactividad del formaldehído, se compararon las condiciones clásicas de Pictet-Spengler (ácido sulfúrico como catalizador) con las nuestras. La ciclación clásica tuvo lugar para dar **31a**, aunque con un modesto rendimiento del 14% (método i, esquema 3.35), presumiblemente mediante ataque al catión oxonio procedente de la protonación del aldehído. Esta reacción ve casi duplicado su rendimiento cuando transcurre a través de la formación del intermedio de α-amidosulfona (**31a**, 23%, método ii.).



Esquema 3. 36

Sin embargo, cuando el aldehído presenta sustituyentes aromáticos, la ciclación vía Pictet-Spengler clásica prácticamente no tiene lugar (**31b**, método i, 8%) y este rendimiento se ve incrementado al emplear ácido sulfínico aunque el impedimento estérico tan elevado que se produce entre el anillo A, el anillo aromático del aldehído y el grupo tosilo, en el intermedio de la reacción, dificulta que se obtenga la planaridad requerida para la formación del catión iminio (esquema 3.37).



Esquema 3. 37

Con respecto al efecto del sustituyente del nitrógeno puente, se puede apreciar que un grupo aceptor de electrones disminuye la densidad electrónica de la lactama lo que conduce a la imposibilidad de generar el catión iminio y ciclación del anillo B a través de la formación de α-amidosulfonas.

En un intento de mejorar los rendimientos realizamos diversos ensayos con *p*-bromobenzaldehído y propanal que quedan recogidos en la tabla 3.9. Desafortunadamente, ninguna de estas condiciones dio lugar a los productos deseados.

Condiciones	R	Rdto%
HOAc/H_2SO_4 (t.a., 45, 60, 120 ºC), 12 h, *p*-BrC_6H_4CHO	CH_3SO_2-	-
HOAc/H_2SO_4 (t.a., 45, 60, 120 ºC), 12 h, Propanal	CH_3SO_2-	-
1.NaH, 1 h., THF anh., t.a., 2.Propanal, TMSCl, TEA.	CH_3SO_2-	-
1.DIPEA, TMSOTf, THF, 1 h, t.a., 2.Propanal, TMSOTf, THF anh.*	CH_3SO_2-	-
1.TMSCl, TEA. 2.Propanal, $TolSO_4$, t.a.	CH_3CO-	-

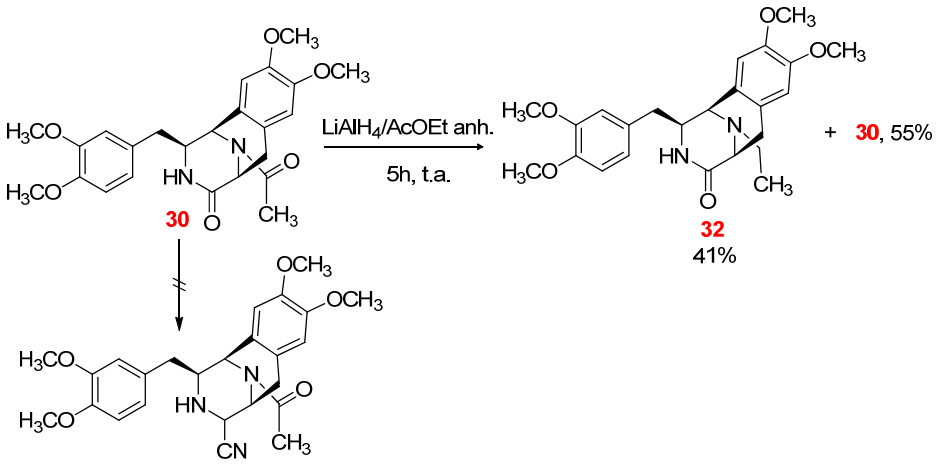
*Reacción realizada también a 45 °C

Tabla 3. 7

Todos los intentos de formar el núcleo pentacíclico de las saframicinas dieron como resultado la descomposición parcial del producto de partida, junto con la recuperación de una parte del mismo sin modificación alguna. Hemos intentado, sin éxito, incrementar la nucleofilia del nitrógeno perteneciente al enlace amida mediante la formación de un silil éter de lactima,[96] combinada con un incremento de la electrofilia del carbonilo del aldehído correspondiente, usando triflato de trimetilsililo en medio básico. También fallaron todos nuestros intentos de llevar a cabo la reacción de Pictet-Spengler en las condiciones clásicas.

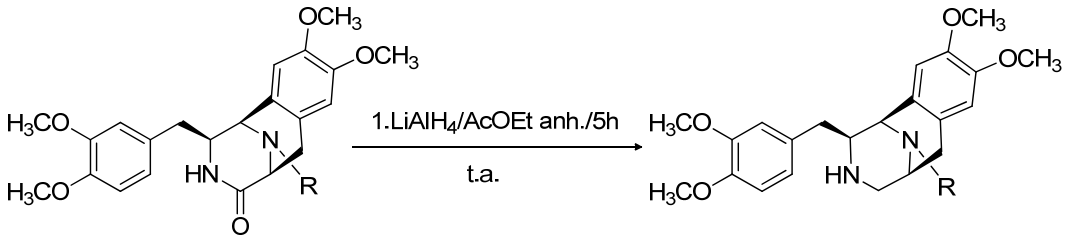
En vista del poco éxito de todos los ensayos realizados, se optó por reemplazar el grupo funcional de lactama por un α-aminonitrilo. Para prepararlo, se intentó reducir el carbonilo al correspondiente hemiaminal mediante la generación *in situ* de hidruro de litio y dietoxialuminio como donador de hidruro,[97] con intención de lograr la posterior sustitución nucleófila del hidroxilo por un cianuro.
Estas condiciones condujeron en el compuesto **30** a la reducción del carbonilo del acetilo, que debido a su accesible disposición espacial, recibe el ataque nucleófilo del $(AcO)_2LiAlH_2$, dando lugar al compuesto **32** (41%) junto con material de partida (**30**, 55%) (esquemas 3.38).

[96] Ortín, I.; González, J. F.; de la Cuesta, E.; Perona, R.; Avendaño, C. *Bioorg. Med. Chem.* **2008**, *16,* 9065.
[97] González, J. F.; de la Cuesta, E.; Avendaño, C *Bioorg. Med. Chem.* **2007**, *15,* 112.



Esquema 3. 38

En paralelo, se realizaron ensayos con los compuestos **26a** y **26b**, que presentan, respectivamente, grupos mesilo y Boc en el nitrógeno del puente, pero en estos casos se obtuvieron los productos totalmente reducidos en el grupo de lactama de la posición 4 (esquema 3.39, Tabla 3.8).

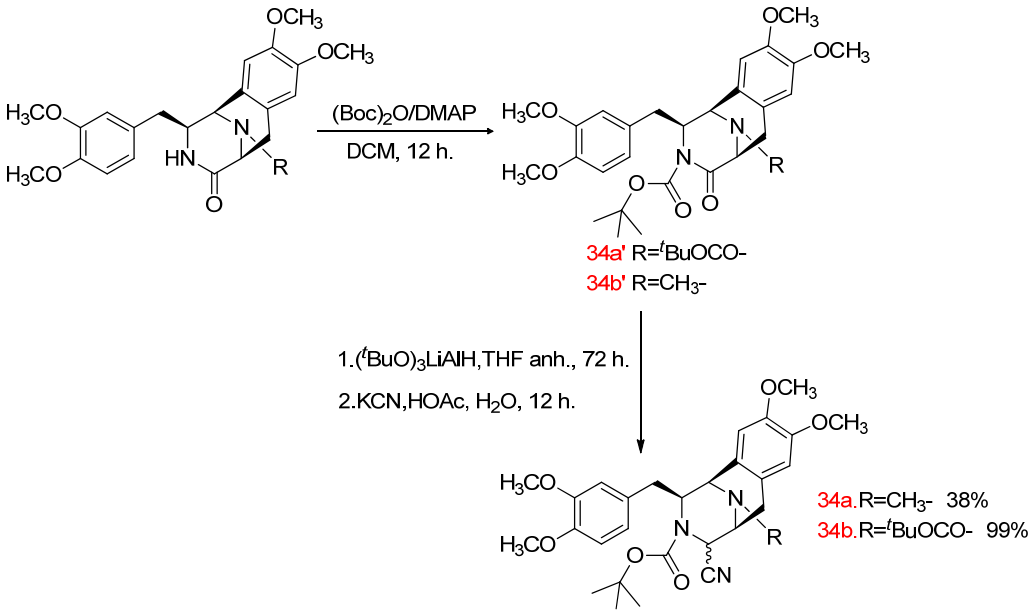


Esquema 3. 39

Compuesto	R	Rdto.%
33a	CH_3SO_2-	56
33b	^{t}BuOCO-	76

Tabla 3. 8

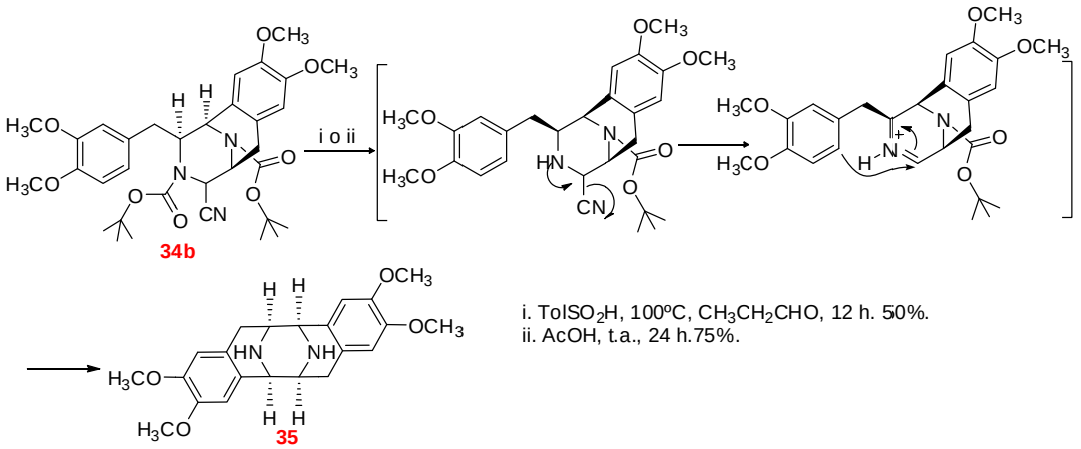
En un intento de solucionar este problema, decidimos activar el carbonilo lactámico formando la correspondiente imida por introducción de un grupo *terc*-butoxicarbonilo en el nitrógeno. Empleando un donador de hidruros impedido, se logró la transformación deseada, que fue seguida de la adición de cianuro potásico en medio ácido (esquema 3.40).



Esquema 3. 40

El compuesto **34b**, obtenido con rendimiento cuantitativo, se sometió finalmente a nuestras condiciones de ciclación habituales (apartado 3.2.2.5), que confiábamos permitieran la desprotección inicial *in situ* del grupo BOC. Esta desprotección tuvo lugar, pero la reacción no siguió el curso esperado y dio lugar al compuesto **35** (esquema 3.41). Este pentaciclo proviene de la hidrólisis del carbamato seguida del ataque directo del anillo aromático sobre el carbono del catión iminio que se genera por eliminación del grupo ciano en el transcurso de la reacción, en lugar de producirse la ciclación esperada con el aldehído a través de la amidosulfona. Hay que destacar la labilidad del grupo ciano en este tipo de estructuras tricíclicas, que contrasta con la estabilidad en condiciones ácidas[98] que presentan los sistemas pentacíclicos de saframicinas con una función análoga.

[98] Antecedente: Cuevas, C.; Pérez, M.; Francesch, A.; Fernández, C.; Chicharro, J. L.; Gallego, P.; Zarzuelo, M.; Manzanares, I.; Martín, M. J.; Munt, S. patente C07D 515/22, **2001** (Pharma Mar).



Esquema 3. 41

Este tipo de estructuras presenta una interesante geometría espacial deducida de la metodología que hemos seguido para alcanzar los distintos pasos de reacción. La estructura imita la de una cesta molecular en la que los dos nitrógenos quedan hacia un mismo lado del plano dejando dos estructuras aromáticas hacia el lado opuesto a modo de cavidad (figura 3.2). Este tipo de estructuras fue estudiado por nuestro grupo y queda recogido en un trabajo paralelo.[99]

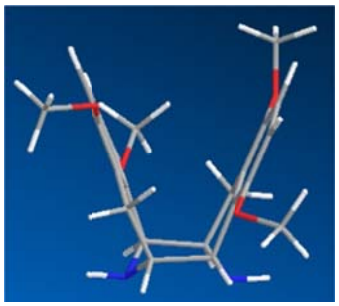
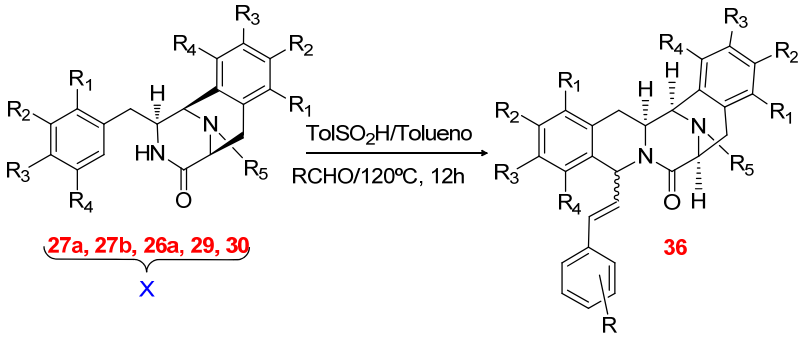


Figura 3. 2

En vista de que no habíamos podido favorecer la ciclación del anillo B aumentando la nucleofilia del nitrógeno de amida, decidimos disminuir el impedimento estérico en el aldehído introduciendo una cadena espaciadora entre el anillo aromático que pretendemos incorporar y el nitrógeno responsable de la formación del acilimino para conseguir así una menor compresión estérica en la ciclación del anillo B. Escogimos con este propósito el

[99] Trabajo experimental fin de Máster Portillo, S. ``Síntesis de una nueva familia de cestas moleculares´´, **2012**.

trans-cinamaldehído y ensayamos las condiciones basadas en la formación de una α-amidosulfona (apartado 3.2.2.5):



Esquema 3. 42

	Compuesto	R	R_5	[X] M	Rdto. %*cis/trans*
R_2, R_3=-OCH_3, R_1,R_4= H	36b/a[1]	H-	CH_3-	0.12	41/16
	36c/d[2]	*o*-NO_2-	CH_3-	0.12	40/40
	36e/f	*p*-Cl-	CH_3-	0.12	25/58
	36g/h	*p*-C_6H_4-	CH_3-	0.24	71/10
	36j/i	*o*-OCH_3-	CH_3-	0.15	25/0
	36j/i	*o*-OCH_3-	CH_3-	0.06	0/36
	36m/k	*p*-OCH_3-	CH_3-	0.24	24/24
	36o/n	*p*-NO_2	CH_3-	0.24	47/16
	36p	H-	CH_3CO-	0.12	26/0
	36q	H-	CH_3SO_2-	0.18	30/0
R_1, R_4= -OCH_3 ,R_2,R_3= H	36r	H-	CH_3-	0.12	33/0
	36s[3]	H-	CH_3-	0.12	71/0

(1) A 110 °C se recupera 99% de material de partida. (2) La mezcla del diasteroisómero *trans* y el *cis* no se consigue separar tras varios intentos de purificación. El rendimiento se calcula sobre la mezcla de ambos. (3) Usamos como compuesto de partida **29** (epímero en C2 de **28b**).

Tabla 3. 9

El uso de cianamaldehído e intermedios de α-amidosulfonas, nos conduce a la ciclación del anillo B de las saframicinas como una mezcla de diasteroisómeros los cuales son determinados mediante el efecto NOE que presentan.

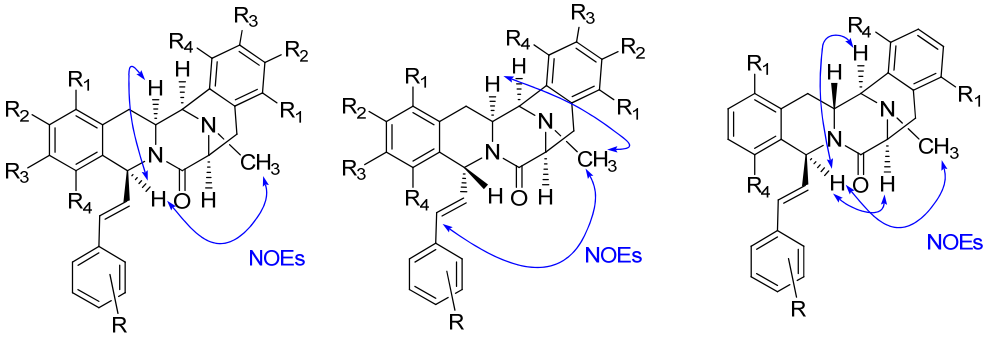
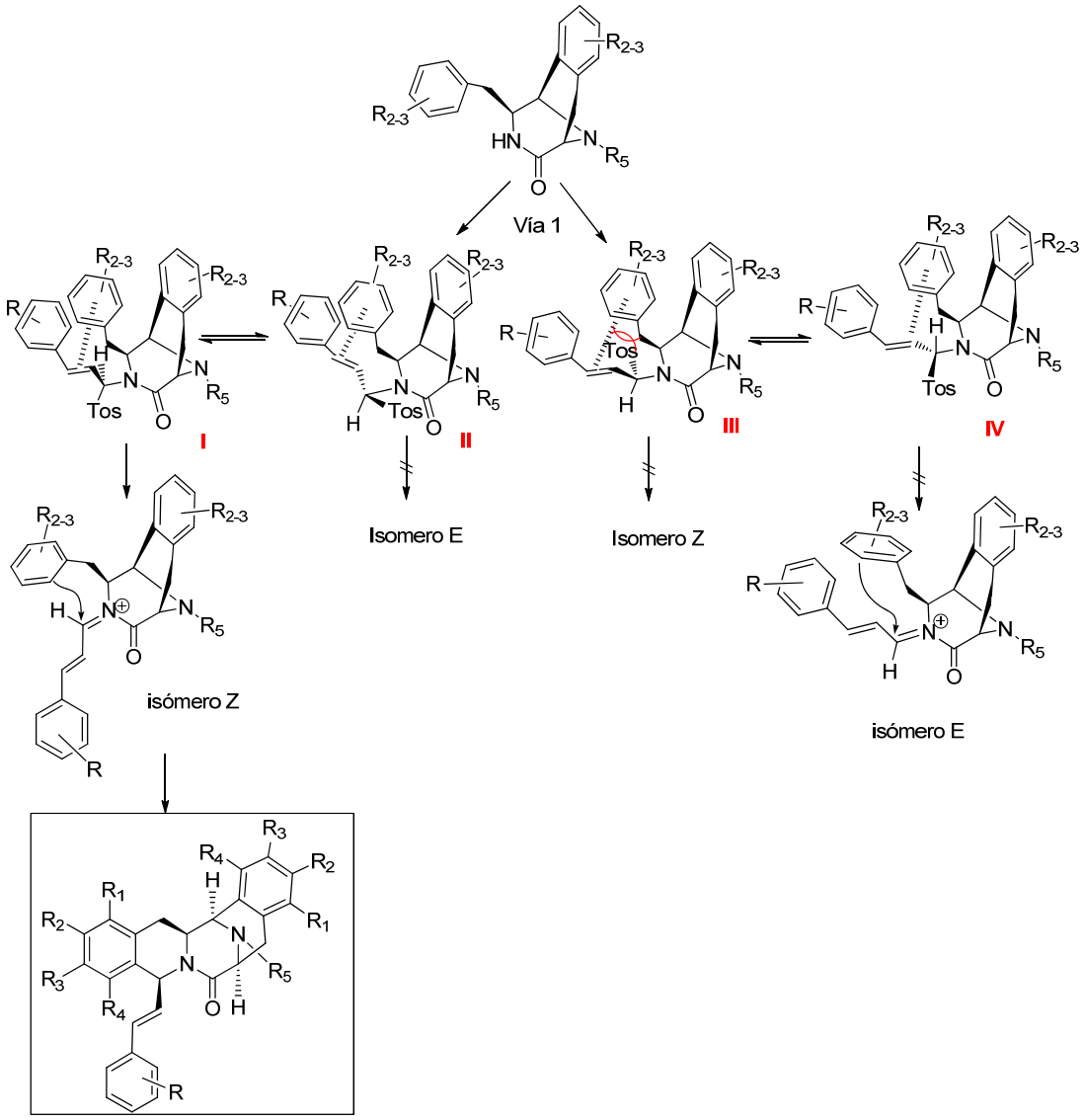


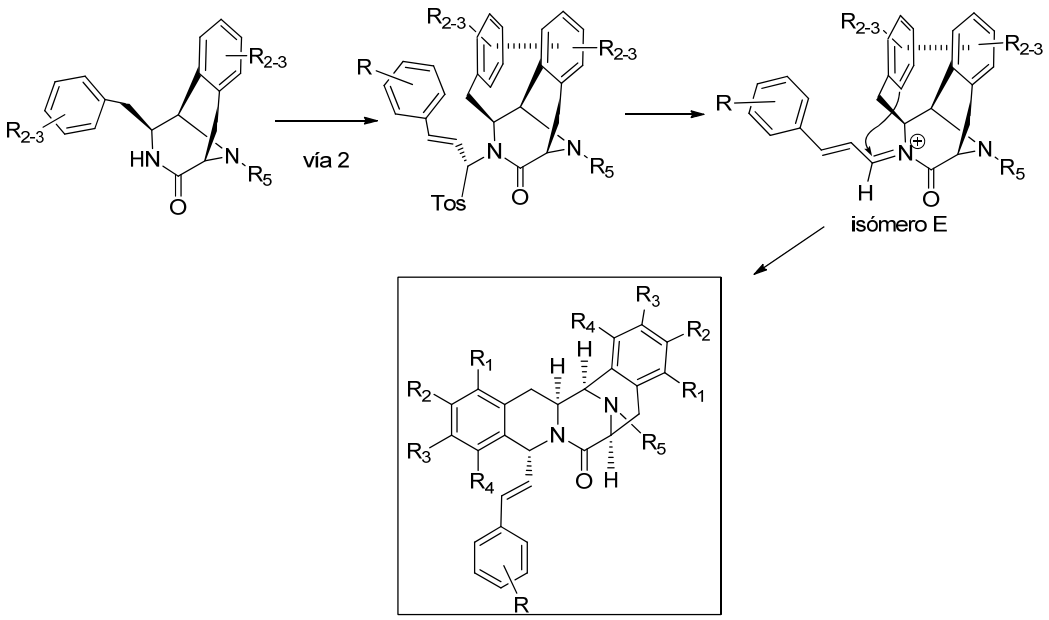
Figura 3. 3

Para poder explicar la diferente estereoquímica del proceso debemos recurrir a los intermedios generados en las distintas interacciones de π-stacking posibles (esquema 3.43 y 3.44). La existencia de interacciones de π-stacking entre el anillo A y la insaturación vinílica, en el intermedio de α-amidosulfona, conduce al diastereoisomero *cis* (vía 1, esquema 3.43). Así, siguiendo el razonamiento expuesto en la obtención del isómero *cis* en los compuestos **16**, el π-stacking en el intermedio **I** es el único que conduce a la estereoquímica deseada (*cis*). Aunque el intermedio **III** debería conducir de igual forma al aciliminio Z, el impedimento estérico entre el tosilo y el anillo A imposibilita la disposición antiperiplanar necesaria. Por otro lado las disposiciones de los intermedios **II** y **IV** que podrían generar los diasteroisómeros *trans*, quedan fijadas por las interacciones π-stacking lo que evita la formación del catión aciliminio, al no poder disponer de forma antiperiplanar el grupo tosilo al par de electrones del nitrógeno.



Esquema 3. 43

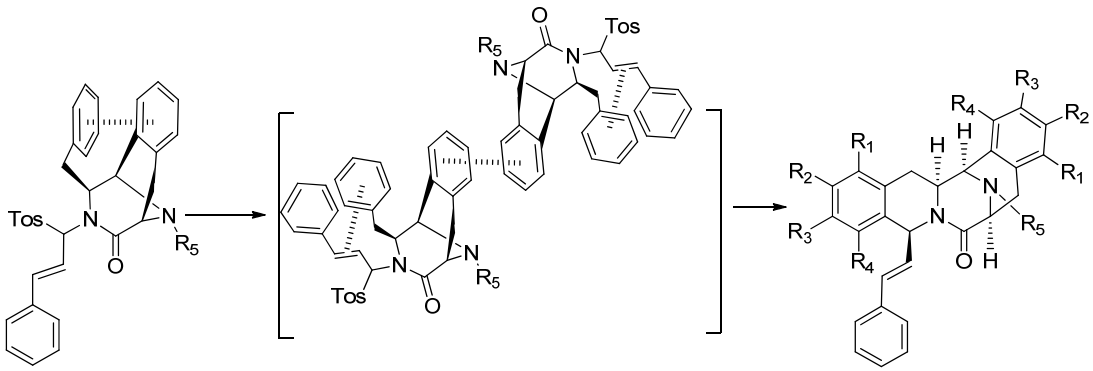
Por otro lado en la vía 2, esquema 3.44, las interacciones de π-stacking entre los anillos aromáticos correspondientes a los ciclos E y A conducirían a la formación de los isómeros *trans*, debido a la libertad de giro en el intermedio de α-amidosulfona que dispone el catión iminio en la conformación *E*. Esta misma disposición espacial es la que conducía en los compuestos **21** a la configuración *trans*.



Esquema 3. 44

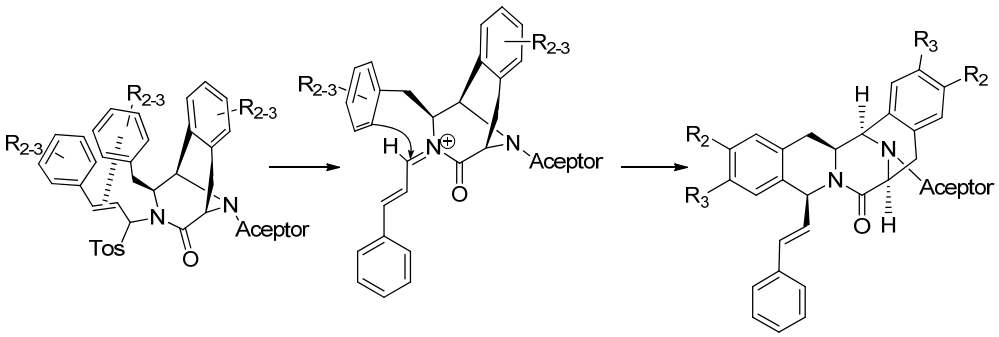
Esta diastereoselectividad puede ser en parte dirigida hacia uno u otro isómero mediante la modificación de las concentraciones. Así, utilizando disoluciones más concentradas se consigue favorecer la formación del compuesto *cis*. En algunos casos hemos logrado alcanzar una total diastereoselectividad (**36j**, *cis*, o **36i**, *trans*), mientras que en otros casos sólo se consigue enriquecer la mezcla (**36g**, **36h**).

Para comprender el efecto de la dilución sobre la diastereoselectividad hemos de proponer interacciones intermoleculares entre los ciclos E, lo que impide el π-stacking intramolecular entre los anillos A y E. Queda así libre el anillo A para establecer una interacción con la función vinílica del estirilo lo que conduce (esquema 3.45) al isómero *cis*.



Esquema 3. 45

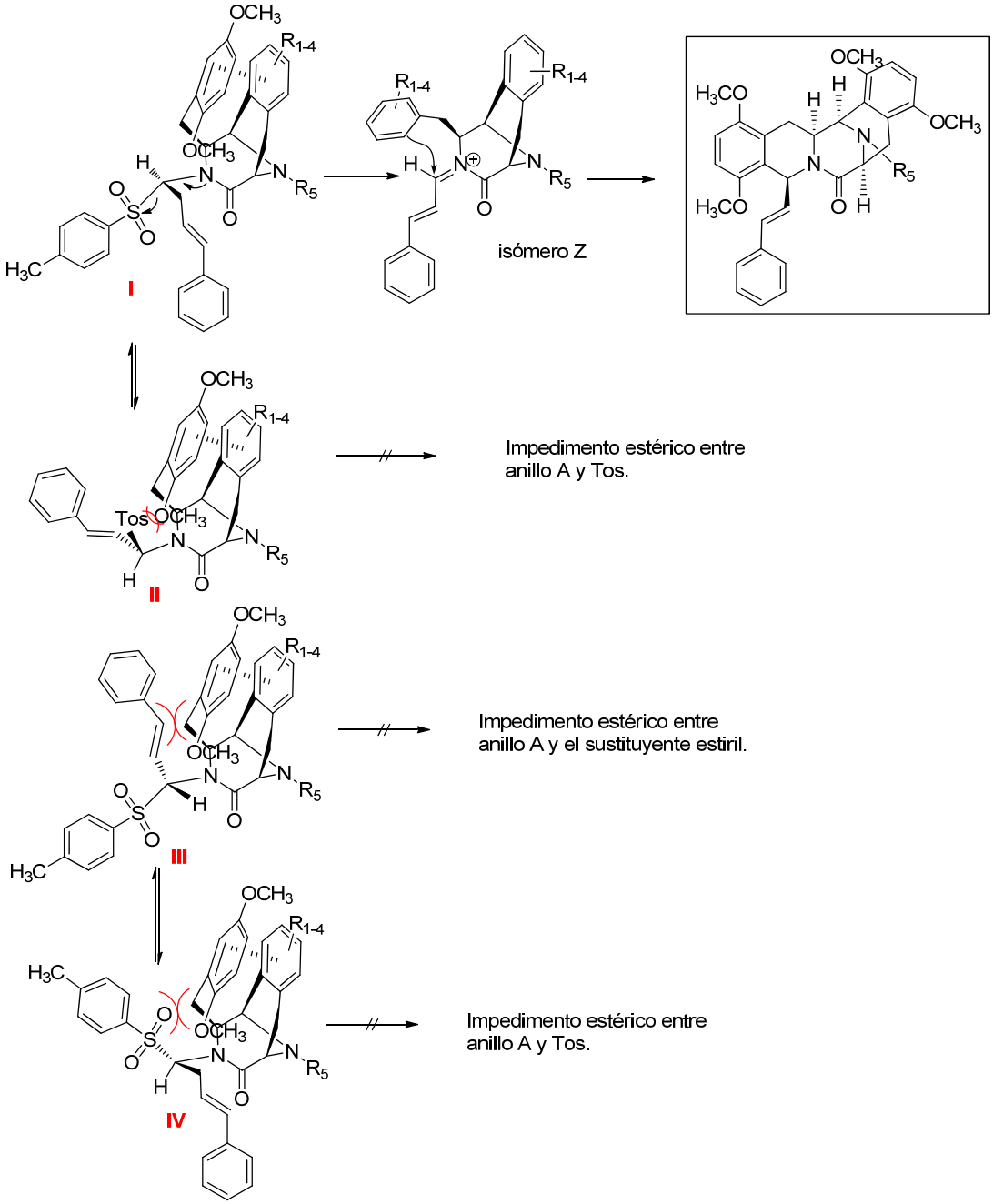
Como ya se vio en los compuestos **30** y **26a** el uso de grupos electroatractores en el nitrógeno del puente afecta a la reacción, al disminuir la densidad electrónica de la estructura. En estas estructuras ese déficit electrónico nos proporciona la diasteroselectividad adecuada (**36p**, **36q**), al romper la interacción de stacking entre los anillos aromáticos A-E lo que deja libertad al anillo A para establecer la interacción de stacking con la insaturación vinílica, dirigiéndonos, a través de la formación del catión aciliminio *Z*, al diasteroisómero *cis* (esquema 3.46).



Esquema 3. 46

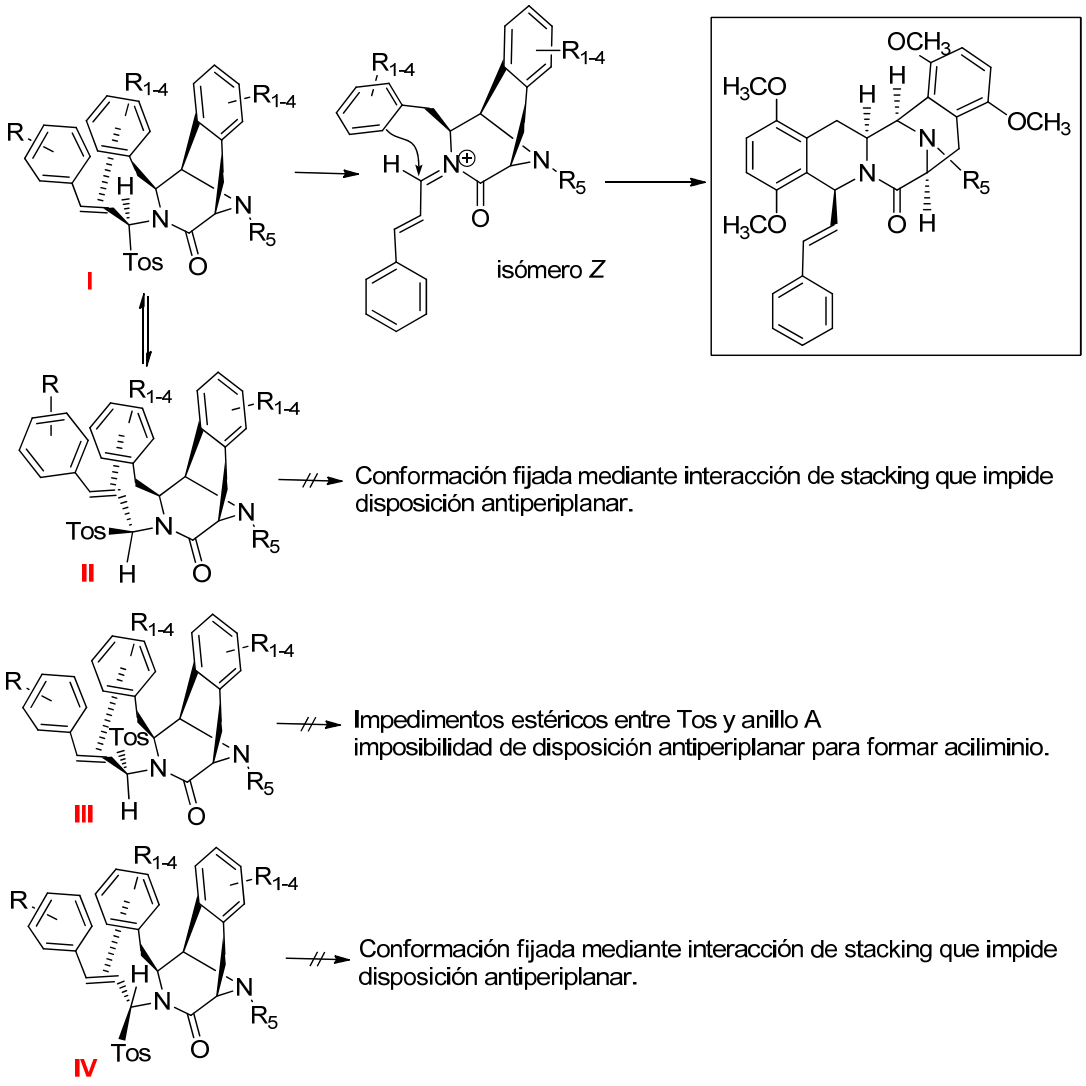
Cuando el nitrógeno de amina no presenta sustituyentes aceptores de electrones se puede producir el π-stacking entre los anillos A y E a la vez que la interacción entre A y la insaturación vinílica que conduce al isómero *cis*, como ya habíamos indicado. Cuando los grupos metoxi que están en el C1 y C4 (en comparación con la sustitución en C2 y C3 del anillo A en el compuesto **36a/b**) podemos encontrar que, excepcionalmente el stacking entre el anillo A y E no conduce al diasteroisómero *trans* ya que aparece un impedimento

estérico que no permite el giro necesario para la colocación *anti* entre el par de electrones del nitrógeno y el grupo tosilo que generaría el diasteroisómero *trans* **36r**. De esta forma la única conformación estable posible es la que conduce al aciliminio *Z* y por tanto al isómero *cis* (esquema 3.47).



Esquema 3. 47

De la misma forma, la otra posible interacción π que se establece entre el anillo A y la insaturación vinílica nos conduciría a la formación del aciliminio *Z* en el intermedio **I**, mientras que el intermedio **III** no podría alcanzar esta misma disposición por los impedimentos estéricos que surgen entre el grupo tosilo y el anillo A en el intento de disposición antiperiplanar. En los intermedios **II** y **IV** quedan fijadas las conformaciones debido al π-stacking lo que imposibilita alcanzar la disposición antiperiplanar y por consiguiente la inviabilidad de la evolución al catión aciliminio.

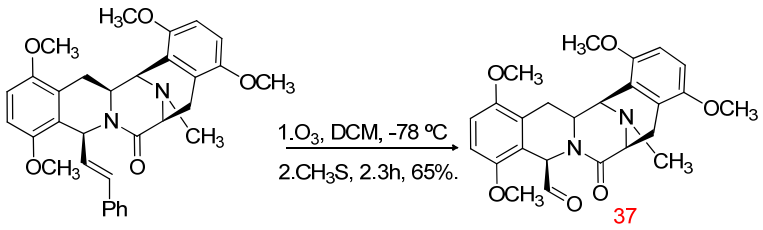


Esquema 3. 48

Por tanto cuando se encuentra sustituido el anillo A en R_1 y R_4 por grupos metoxi la única disposición posible es la que conduce al diastereoisómero *cis*.
Por último, es de destacar que cuando la reacción se lleva acabo con el compuesto epimerizado en C2 (**36s**), se obtiene un rendimiento muy superior a los casos anteriormente estudiados. Podemos atribuir esta diferencia a la tensión estructural a la que está sometida el núcleo pentacíclico, que presenta la estereoquímica de las saframicinas, que desaparece cuando el anillo A se coloca a distinto lado del plano que el anillo E.

3.2.3.7. Funcionalización del grupo estirilo.

La necesidad de transformar el estirilo en un grupo funcional que nos permitiera alcanzar los sustituyentes presentes en los compuestos naturales nos condujo a practicar una reacción de ozonolisis sobre la insaturación del sustituyente en C9. Se obtuvo el compuesto **37**, muy inestable.



Esquema 3. 49

3.2.3.8. Conclusiones de la estrategia sintética ACEDB.

-La reducción regioselectiva de los compuestos dicondensados presenta un serio problema cuando se aplica sobre anillos A y E muy sustituidos.
-La formación del carbamato de *terc*butilo de forma selectiva sobre una de las posiciones amida constituye un problema a la hora de una síntesis lineal al tener que forzar la disminución del rendimiento para alcanzar la regioselectividad deseada.
-La obtención del anillo D ha sido optimizada mediante el uso del ácido trifluoroacético como promotor ácido.
-Las condiciones de reducción del doble enlace exocíclico en los compuestos **25** están relacionadas con el sustituyente de la función amina y los sustituyentes del anillo A.
-Siguiendo el orden de obtención de los ciclos ACEDB, hemos conseguido alcanzar el pentaciclo deseado con unos rendimientos que oscilan entre moderados a altos empleando un método nunca aplicado en la síntesis de esta familia de alcaloides de origen natural.

Se encuentra una gran dificultad para generar los intermedios α-amidosulfona en los sitemas pentacíclicos y que evolucionen a un catión aciliminio con aldehídos aromáticos, debido al problema estérico.

-El uso de derivados del cianamaldehído, que contienen un espaciador que separa el anillo aromático en los intermedios de α-amidosulfona, relajando la tensión estérica, permite la ciclación del anillo B con rendimientos aceptables.

-La diasteroselectividad proporcionada por el método de obtención de α-amidosulfonas puede explicarse en fución de interacciones de π-stacking. Cuando éstas se producen entre el anillo A y E, se obtiene el diastereoisomero *trans* (salvo cuando los sustituyentes R_1 y R_4 del anillo A son metoxi) y cuando este π-stacking se establece entre el anillo A y la insaturación en el grupo estirilo se llega al diastereoisómero *cis*.

-El incremento del volumen en los sustituyentes R_1 y R_4 del anillo A determina la diastereoselección de la reacción hacia la disposición *cis* tanto cuando existe π-stacking entre los anillos Ay E, como cuando esta interacción se da entre el anillo A y la insaturación en el estirilo. En este caso también se genera una disminución en el rendimiento de la misma.

-La sustitución del grupo amino con grupos que retiren carga afecta directamente, tanto a la estereoquímica (generando el diasteroisómero *cis* de forma diasteroselectiva) como al rendimiento de la reacción (disminuyéndolo).

-La introducción de un grupo estirilo en C9 nos proporciona la posibilidad de alcanzar análogos de las saframicinas, a través de la ruptura oxidativa de la insaturación vinílica.

3.3. Aplicación de las α-amidosulfonas a la síntesis del esqueleto de las saframicinas. Estrategia ACE-B-D.

3.3.1. Preparación del sistema ACE.

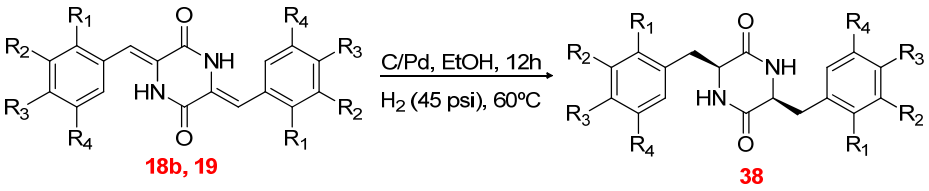
3.3.1.1. Antecedentes.

El primero en plantear una secuencia sintética conteniendo inicialmente los anillos ACE, de forma simétrica, fue Liebeskind[100] en 1991. Posteriormente, Ong[101]emuló está misma estrategia, aunque cada uno siguió rutas diferentes en el orden de obtención de los ciclos contenidos en las saframicinas. El aprovechamiento de la simetría inherente a muchas de las saframicinas naturales aporta una dificultad añadida a la metodología, obligando a llevar a cabo un paso de reacción regio- y diastereoselectivo. Por otro lado, la ruta que mantiene la ciclación del anillo D como último paso en la obtención del núcleo de la saframicina ha sido seguida por varios grupos de investigación, aunque sin partir de un precursor simétrico. Algunos de estos grupos han planteado una síntesis convergente a través de la formación de los anillos CD usando como precursores *cis*-tetrahidroisoquinolinas 1,3-disustituidas[102] o 1,4-disustituidas[103] mientras que otros han abordado una síntesis lineal mediante la alquilación en C3 de derivados de pirazino[1,2-*b*] isoquinolinas[104].

3.3.1.2. Reducción total de los compuestos dicondensados.

Para la preparación del sistema ACED nos propusimos practicar una reacción de ciclación sobre el sistema completamente reducido ACE con la esperanza de que ésta se produjera de manera selectiva en uno de los dos anillos. La ventaja que presenta esta estrategia al tener ya reducida la otra posición bencílica, reside en la disminución de pasos en la síntesis total. Para ello, partimos de los compuesto **18b** y **19** y llevamos a cabo la reducción de ambas insaturaciones mediante una hidrogenación catalítica a 60 ºC y 45 psi, obteniéndose cuantitativamente los compuestos **38** (esquema 3.50, tabla 3.10).

[100]Shawe, T. T.; Liebeskind, L. S. *Tetrahedron* **1991**, *47*, 5643.
[101]Chang, Y.; Sun, T.; Chiang, M.; Lu, P.; Huang, Y.;Liang, L. and Ong, C. *Tetrahedron* **2007**, *63*, 8781.
[102]Martínez, E. J.; Corey, E. J. *Org. Lett.* **1999**, *1*, 75.
[103](a) Zhou, B.; Edmondson, S.; Padron, J.; Danishefsky, S. J. *Tetrahedron Lett.* **2000**, *41*, 2039. (b) Zhou, B.; Guo, J.; Danishefsky, S. J. *Tetrahedron Lett.* **2000**, *41*, 2043. (c) Chan, C.; Heid, R.; Zheng, S.; Guo, J.; Zhou, B.; Furuchi, T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 4596.
[104](a) Liu, Z.; Tang, Y.; Chen, S.; Chen, X.; Li, H. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 1282. (b) Ortín, I.; González, J. F.; de la Cuesta, E.; Avendaño, C. *Bioorg. Med. Chem.***2010**, *18*, 6813.



18b, 19 — 38

Esquema 3. 50

	Compuesto	Rdto. %
R_1, R_4= -OCH_3 ,R_2,R_3=H	38a	99
R_1, R_4, R_3= -OCH_3 ,R_2= -CH_3	38b	99

Tabla 3. 10

Como se puede apreciar, no existe relación entre el rendimiento de la reacción y la diferente sustitución de los anillos aromáticos tratándose de una reacción limpia y que transcurre en condiciones muy suaves.

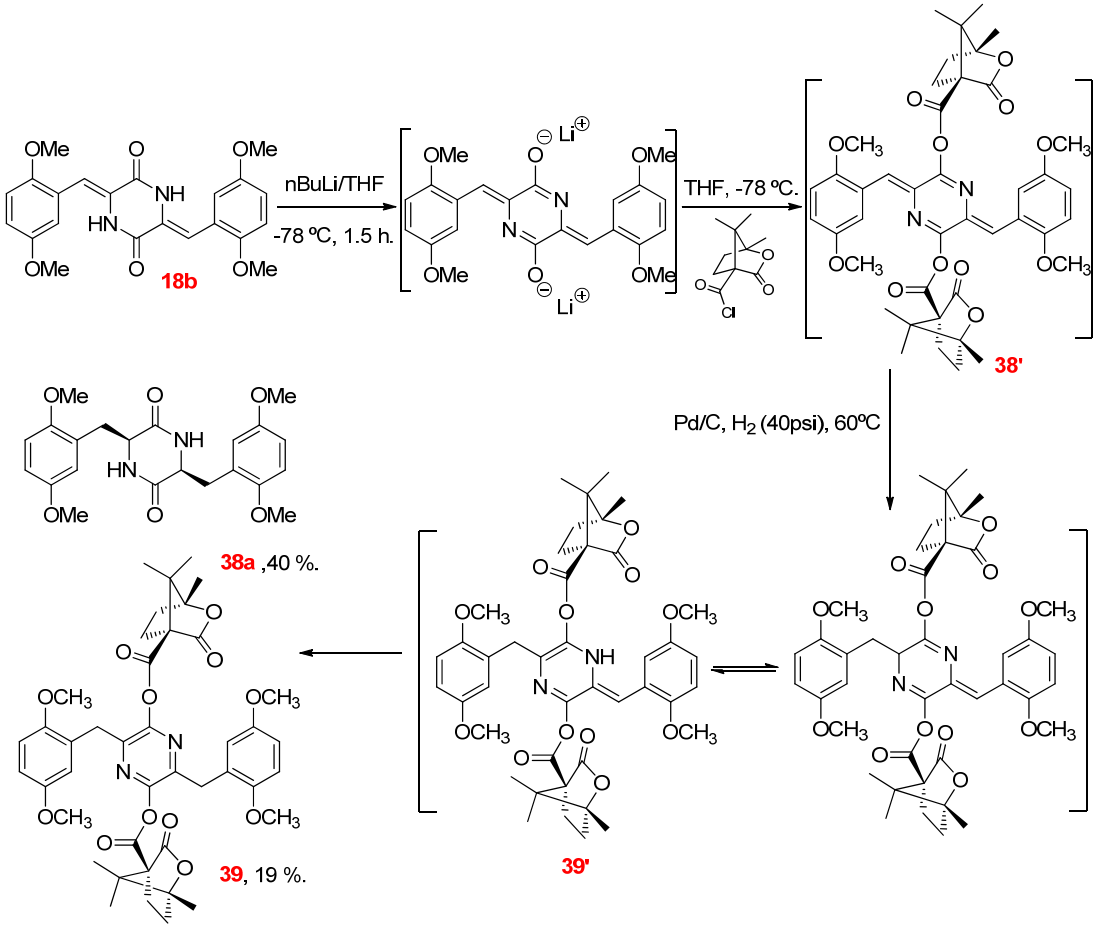
3.3.1.3. Intento de hidrogenación asimétrica en presencia de auxiliares quirales.

El paso de hidrogenación proporciona una oportunidad de lograr una síntesis quiral de los intermedios tetrahidroisoquinolínicos. Por ejemplo, el grupo de Corey realizó esta hidrogenación asimétrica aplicando el catalizador de Monsanto en la síntesis de la (-) Saframicina A[105] bajo las condiciones previamente establecidas por Kagan *et. al.*[106] Aunque no era nuestro objetivo principal, realizamos un intento de hidrogenación asimétrica mediante el empleo de un auxiliar quiral, para lo cual seleccionamos (1*S*)-(-)-cloruro de canfanilo. El tratamiento del compuesto **18b** con butil litio y dos equivalentes del cloruro canfánico condujo presumiblemente al éter de bis-lactima quiral, que, a causa de su baja estabilidad, fue reducido inmediatamente, aislándose los compuestos **38a** y **39** (esquema 3.51). Desafortunadamente, **38a** resultó ser racémico, según demostró un análisis por HPLC en una columna quiral,[107] lo cual puede explicarse de dos formas:

-Una total ausencia de inducción asimétrica en la etapa de hidrogenación.

[105] Martinez, E. J.; Corey, E. J. *Org. Lett.* **1999**, *1*, 75.
[106] Hammadi, A.; Nuzillard, J.M.; Poulin, J.C.; Kagan, H.B. *Tetrahedron: Asymmetry* **1992**, *10*, 1247.
[107] Agradecemos a Nicolas Vanthuyne, de la Universidad de Marsella, la realización de este estudio.

-Una formación incompleta del éter de bis-lactima quiral, de modo que lo que redujimos fue una mezcla de compuesto de partida **18b** (que proporcionó **38a** racémico) y el intermedio quiral, que dio **39** por hidrogenación de uno de los dobles enlaces exocíclicos seguida de isomerización del otro, favorecida por la aromatización del sistema heterocíclico.

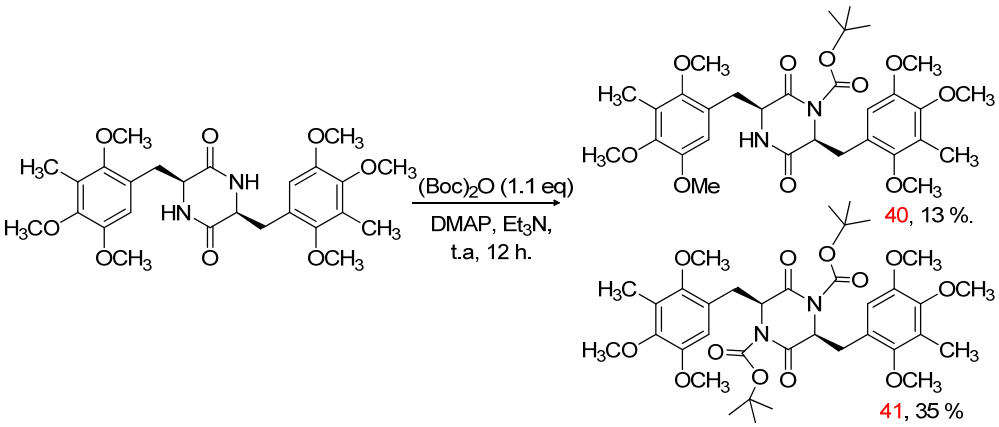


Esquema 3. 51

3.3.1.4. Síntesis de carbamatos en el compuesto 38.

Hicimos un intento de acilación selectiva de uno de los nitrógenos del derivado de bisbencilpiperazinadiona **38**. Esto nos permitiría tanto un acercamiento rápido a la ruta sintética ACEDB como la apertura de una alternativa en la ruta ACEBD. A pesar del empleo de una cantidad equimolar de dicarbonato de di*terc*butilo, no fue posible lograr un

rendimiento aceptable del producto de monoacilación **40**, siendo mayoritario **41** (esquema 3.52), por lo cual se abandonó esta aproximación.



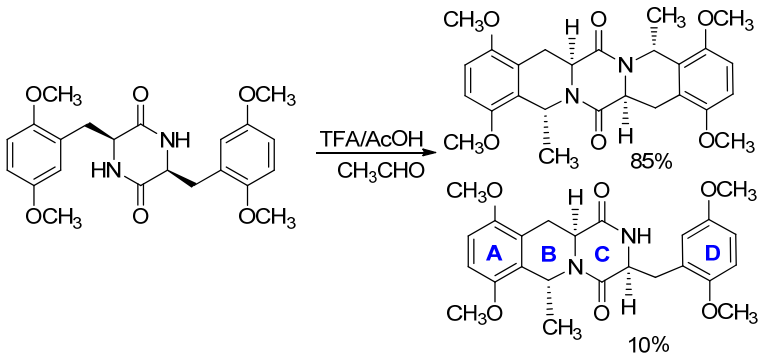
Esquema 3. 52

3.3.2. Preparación del sistema ACE-B.

3.3.2.1. Antecedentes.

Debido a la dificultad que entraña lograr una reacción que reúna las condiciones de regio y diastereoselectividad en un sólo paso, es escasa la bibliografía encontrada en este punto y la única referencia que hay hasta el momento en la síntesis de estructuras relacionadas con las saframicinas[108] utiliza una reacción de ciclación clásica de Pietet Spengler, que proporciona una mezcla de pirazino[1,2-*b*]isoquinolinas y tetrahidropirazino[1,2-*b*:4,5-*b*']diisoquinolinas, ambas con la estereoquímica C6-C11a *trans.*

[108]Chang, Y.; Sun, T.; Chiang, M.; Lu, P.; Huang, Y.;Liang, L. and Ong, C. *Tetrahedron*,**2007**, *63*, 8781.

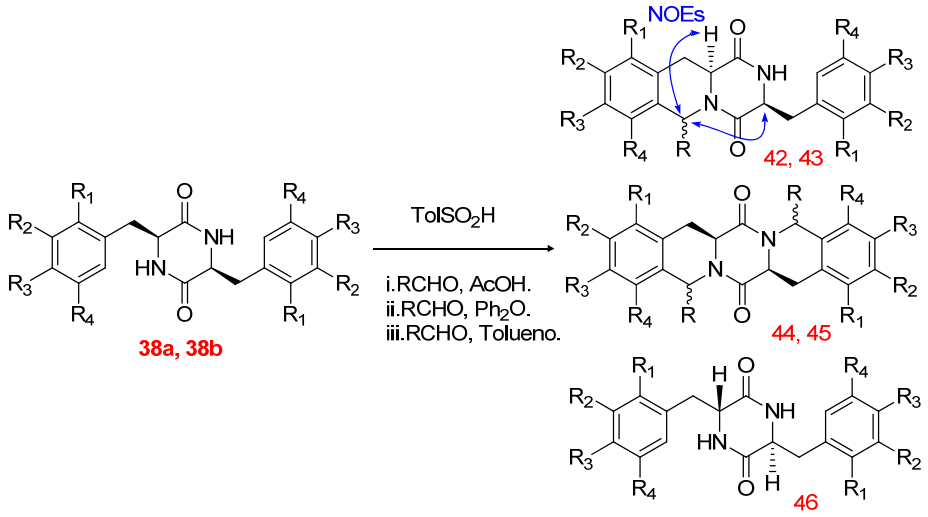


Esquema 3. 53

3.3.2.2. Ciclación del anillo B mediante intermedios de α-amidosulfonas.

Aplicando la síntesis de tetrahidroisoquinolinas a través de intermedios de α-amidosulfona, puesta a punto para la obtención del anillo B, intentamos alcanzar unas condiciones que rindiesen las exigencias de este paso de reacción, donde se requiere una disposición relativa *cis* entre las posiciones C6-C11a.

Cuando la reacción de ciclación no tiene lugar y se prolongan los tiempos de reacción obtenemos la epimerización de H6 (**46**), mientras que los compuestos ciclados no presentan esta particularidad como demuestran los efectos NOE encontrados.



Esquema 3. 54

	Entrada	Condiciones	R	Rdto. % 42, 43 *cis/trans* H6-H11a	Rdto. % 38, 46	Rdto. % 44, 45 *cis/trans* *H8-H16*
R_1,R_4=OCH_3, R_2,R_3= H	(1)	i.TolSO_2H(1.0 eq), 120 ºC, 12 h.	Ph-	-/**42a**(67)	**38a**(9)	**44a**(12)/-
	(2)	i.TolSO_2H (2.0 eq), 120 ºC, 12 h.	Ph-	-/**42a**(29)	-	**44a**(37)/**44b**(7)
	(3)	i.TolSO_2H (1.0 eq), 120 ºC, 24 h.	*m*-NO_2 C_6H_4-	-	**46**(52)	-
	(4)	i.TolSO_2H (1.0 eq), 120 ºC, 24 h.	PhCHCH-	-/**42b**(46)	-	**44c**(31)/-
	(5)	ii.TolSO_2H (1.0 eq), 120 ºC, 3 h.	PhCHCH-	-/**42b**(44)	-	**44c**(34)/-
	(6)	ii.TolSO_2H (1.0 eq), 90 ºC, 3 h.	PhCHCH-	-/**42b**(39)	**38a**(35)	**44c**(19)/-
	(7)	ii.TolSO_2H (1.5 eq), 110 ºC, 12 h.	PhCHCH-	-/**42b**(65)	**38a**(10)	**44c**(20)/-
	(8)	iii.TolSO_2H (1.0 eq), 120 ºC, 3 h.	PhCHCH-	-/**42b**(38)	**38a**(11)	**44c**(39)/-
	(9)	iii.TolSO_2H (2.8 eq), 120 ºC, 12 h.	PhCHCH-	-	-	**44c**(80)/-
R_1, R_4, R_3=OCH_3, R_2= CH_3	(10)	ii. TolSO_2H (1.5 eq), 110 ºC, 6 h.	PhCHCH-	**43a**(59)/-	-	**45**(39)/-
	(11)	ii. TolSO_2H (1.5 eq), 140 ºC, 6 h.	PhCHCH-	-	-	**45**(98)/-
	(12)	iii.TolSO_2H (1.1 eq), 115 ºC, 5.5 h.	PhCHCH-	**43a**(40)/-	**38b**(50)	-
	(13)	iii.TolSO_2H (1.1 eq), 115 ºC, 24 h.	$PhCH_2CH_2$-	-/**43b**(20)	-	-

Tabla 3. 11

De los resultados obtenidos al aplicar las diferentes condiciones podemos concluir que es posible llegar a conseguir una síntesis regioselectiva y diastereoselectiva, no alcanzada hasta el momento en ninguna aproximación a los nucleos pentacíclicos, siguiendo esta nueva vía de síntesis. Los factores que influyen en la reacción son:

-La naturaleza del disolvente. Encontramos un rendimiento superior con el uso de difenil éter en los compuestos con sustituyentes metoxi en C1 y C4 que en los derivados con la sustitución presente en los compuestos naturales, en los que el disolvente con mejores resultados fue el tolueno.

-La temperatura y el tiempo empleados han sido factores importantes, para un mismo sustrato (entradas 5, 7). Encontramos que el incremento tanto de la temperatura como del tiempo genera mayores rendimientos.

-Es posible conseguir una diasteroselectividad concreta a través de las α-amidosulfonas en función de la sustitución de los anillos A y E (entradas 7, 10), así como del aldehído utilizado para la formación del intermedio (entradas 12, 13).

La diastereoselectividad presente en los compuestos con sustituyentes metoxi en C1 y C4 es *trans* para los aldehídos ensayados. Si atendemos a la disposición espacial de estas estructuras (figura 3.4) vemos que el π-stacking formado entre los anillos A-E, permite libertad de giro al intermedio de α-amidosulfona, haciendo posible la formación del catión aciliminio *E* (diastereoisómero *trans*), con menor impedimento estérico. El mayor alejamiento entre el anillo A y el intermedio de α-amidosulfona, es posible por no existir la rigidez impuesta por el anillo D, como ocurría en el triciclo del esquema 3.47.

Esta situación quedó también puesta de manifiesto en los compuestos **21** que poseían un sustituyente bencilideno en posición 3 en lugar del anillo D.

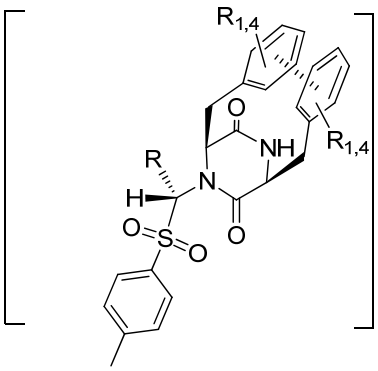
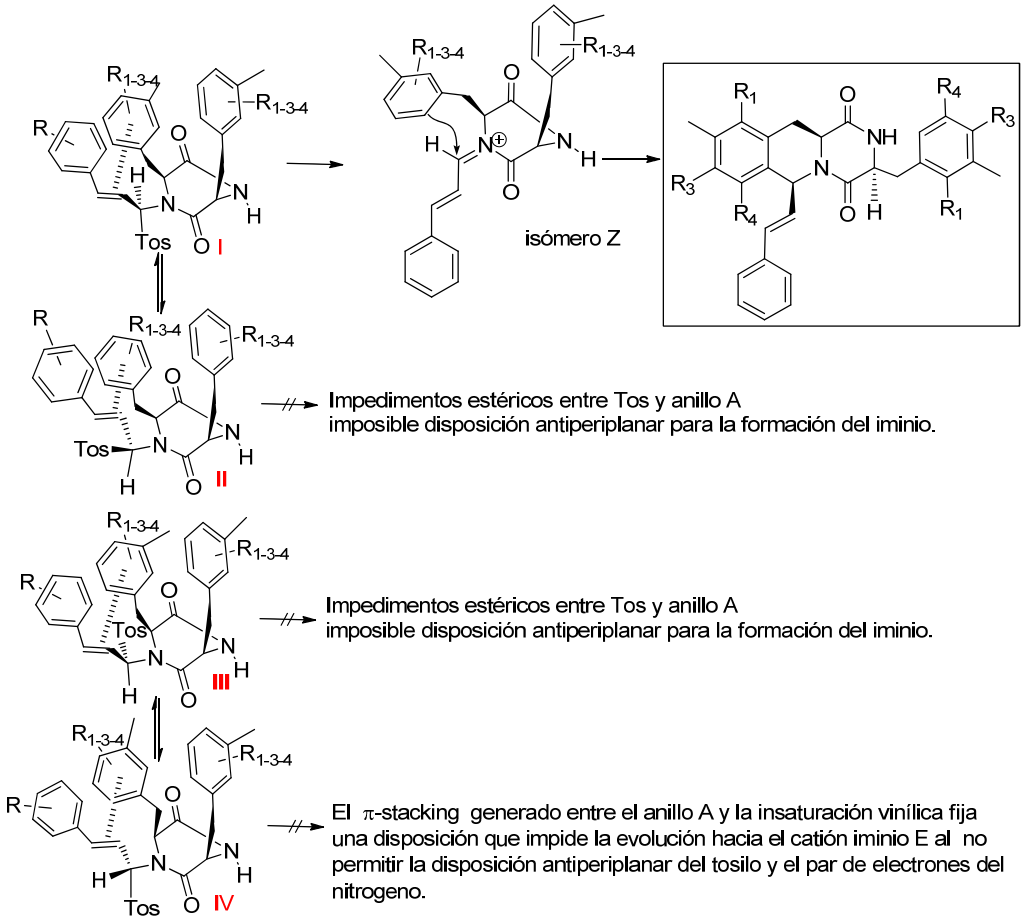


Figura 3. 4

Sin embargo, la sustitución natural da lugar al isómero *cis* cuando el aldehído utilizado es el cianamaldehído (**38b**) (entrada 12, tabla 3.54). La explicación a este fenómeno se puede atribuir al gran volumen que poseen tanto el anillo A como el E, causado por los

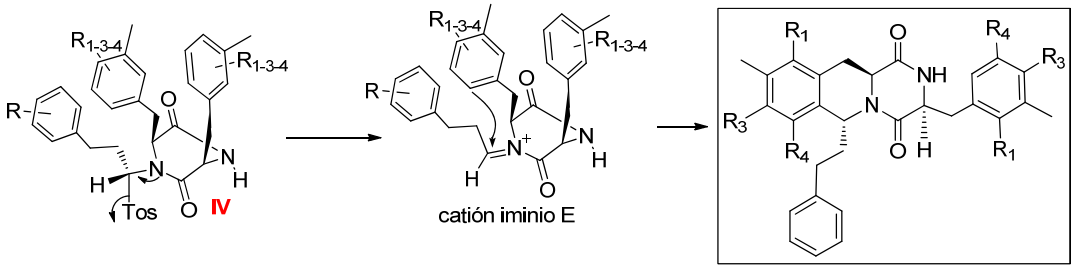
sustituyentes metoxi y metilo, que generan un impedimento estérico que no permite el π-stacking entre ellos, favoreciendo la interacción entre el anillo A y la insaturación vinílica, que conduce al catión iminio *Z*. Las demás posibilidades para el intermedio de α-amidosulfona no conducen al catión iminio por presentar todas impedimento estérico entre el grupo tosilo y el anillo A o bien por fijar una disposición entre el estirilo y el anillo A que impide la disposición antiperiplanar necesaria para la eliminación que lleva al doble enlace del iminio.



Esquema 3. 55

Cuando llevamos a cabo esta misma reacción con 3-fenilpropanal, el diasteroisómero obtenido es el *trans*. Para razonar este hecho debemos atender a la ausencia de insaturación en la cadena alifática por lo que el π-stacking no es posible y el intermedio **I** no quedaría estabilizado, ya que el isómero *Z* que debería formarse es el más impedido estéricamente. De la misma forma que en el caso anterior los intermedios **II** y **III** presentarían los

impedimentos estéricos descritos. En cambio el intermedio **IV** al no encontrar la posibilidad de fijar una conformación determinada, por no existir fuerzas de π-stacking, evoluciona a la disposición antiperiplanar entre el tosilo y el par de electrones del nitrógeno generando el catión iminio *E* que produce el diastereoisómero *trans*.



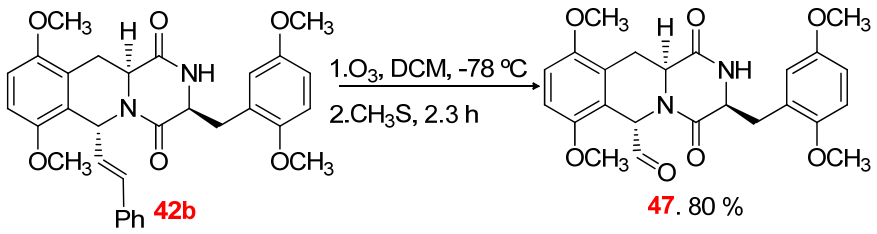
Esquema 3. 56

Mediante el empleo del sustituyente estirilo podemos obtener el ciclo B con la disposición espacial encontrada en los compuestos de origen natural, a la vez que introducimos un grupo que puede ser funcionalizado mediante la ruptura oxidativa del enlace exocíclico contenido en el sustituyente de la posición C6.

Aunque el rendimiento de la reacción no es siempre elevado, el material de partida sin reaccionar puede ser recuperado de forma rápida y usado en posteriores reacciones y además la robustez y escalabilidad de la reacción hacen posible la síntesis mediante este método de pirazino[1,2-*b*]isoquinolina en cantidades suficientes para la continuación de la ruta sintética.
Hasta el momento, ningún grupo de investigación ha planteado con resultados satisfactorios una ruta regio y diastereoselectiva partiendo de un compuesto simétrico de este tipo, lo cual a la vista de los resultados obtenidos por nosotros mediante el empleo de α-amidosulfonas, crea un precedente en la síntesis de núcleos de las saframicinas, abriendo así la puerta a la posibilidad de una nueva ruta sintética.

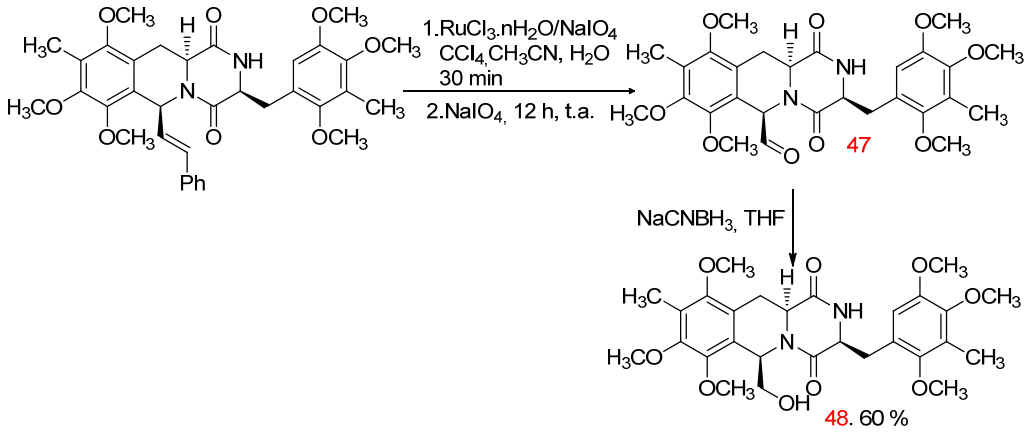
3.3.2.3. Funcionalización del grupo estirilo.

Como ya quedó reflejado en el apartado 3.2.3.7 la ruptura oxidativa mediante el empleo de la ozonolisis rinde el aldehído correspondiente (esquema 3.57).



Esquema 3. 57

Al haber encontrado problemas de falta de reproducibilidad, consideramos necesaria la puesta a punto de un método alternativo. El tratamiento de **43a** con tetraóxido de rutenio generado *in situ*,[109] en un sistema bifásico tetracloruro de carbono: agua: acetonitrilo, y la posterior reducción con cianoborohidruro sódico ofrece el compuesto deseado **48** con un rendimiento global del 60 % (esquema 3.58).



Esquema 3. 58

Los ensayos para la obtención del hidroxi derivado (**48**) cubrieron un amplio espectro de donadores de hidruros. La inviabilidad de todos los reductores a excepción del cianoborohidruro sódico resulto particularmente llamativa.

[109](a) Carlsen, P. H. J.; Katsuki, Y.; Martín, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Núñez, M. T.; Martín, V. S. *J. Org. Chem,* **1990**, *55*, 1928. (c) Martín, V. S.; Palazón, J. M.; Rodríguez, C. M. En "*Encyclopedia of Reagent for Organic Synthesis*". Paquette, L. A. Ed. Wiley: New York, 1995, *Vol 6*, p 4415.

3.3.3. Síntesis del anillo ACE-B-D.

3.3.3.1. Antecedentes.

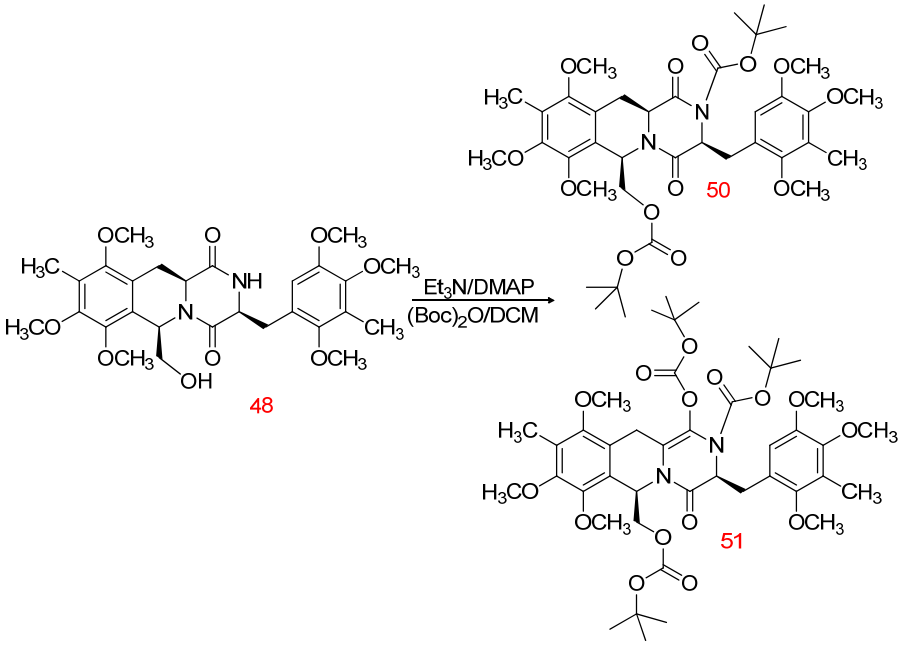
La construcción del sistema de ciclos ABCE y ciclación final del anillo D es una estrategia sintética seguida por varios grupos de investigación. En el año 2005, Magnus *et. al* [110] aplicando estas pautas en la ciclación, desarrollaron la síntesis de la renieramicina G, más tarde el grupo de investigación de Avendaño[111] continuó con esta misma secuencia sintética en la construcción del sistema pentacíclico de análogos de las saframicinas. Aunque no todos los grupos mantienen la secuencia ABCED, son muchos los que han mantenido como último paso la obtención del ciclo D[112]. En todos los casos, este paso de ciclación implica la formación de un catión iminio que se logra tras generar un buen grupo saliente en el C1 y posterior ataque nucleófilo por parte del anillo aromático.

3.3.3.2. Activación del C1.

3.3.3.2.1. Formación del enlace carbamato sobre el compuesto 48.

Siguiendo la misma metodología que la aplicada en el apartado 3.2.3.2, era necesario generar en C1 un carbono con la electrofilia suficiente para el posterior ataque nucleófilo por el sustituyente arilmetilo. Para ello, debilitamos el enlace amida correspondiente por acilación de su nitrógeno con el dicarbamato de di*terc*butilo, para dar **50**. Esta reacción se vio complicada inicialmente con el aislamiento del derivado **51** (esquema 3.59), pero el empleo de cantidades equimoleculares de todos los reactivos permitió aislar **50** con excelente rendimiento (tabla 3.12).

[110] Magnus, P.; Matthews, K. S. *J. Am. Chem. Soc.*, **2005**, *127*, 12476.
[111] Ortín, I.; González, J. F.; De la Cuesta, E.; Avendaño, C. *Tetrahedron*, **2009**, *65*, 2201.
[112] Liao, X.W.; Liu, W.; Dong, W.F.; Guan, B.H.; Chen, S.Z.; Liu, Z.Z. *Tetrahedron*, **2009**, *65,* 5709.



Esquema 3. 59

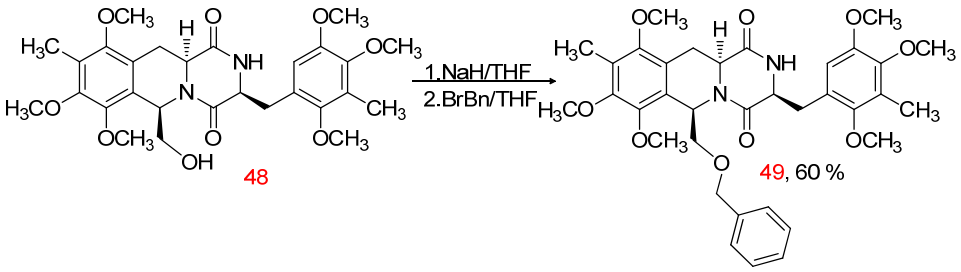
Et_3N/DMAP	Rdto. %
5 eq/ 5 eq	30 (**51**) 60 (**50**)
0.5 eq/ 0.5 eq	86(**50**)

Tabla 3. 12

La explicación de la formación del compuesto **51** se encuentra en el incremento de la acidez del protón H11a, al formar el primer enlace carbamato, por lo que un exceso de base, genera el enolato, que evoluciona al dicarbonato **51** en presencia de un exceso de anhídrido.

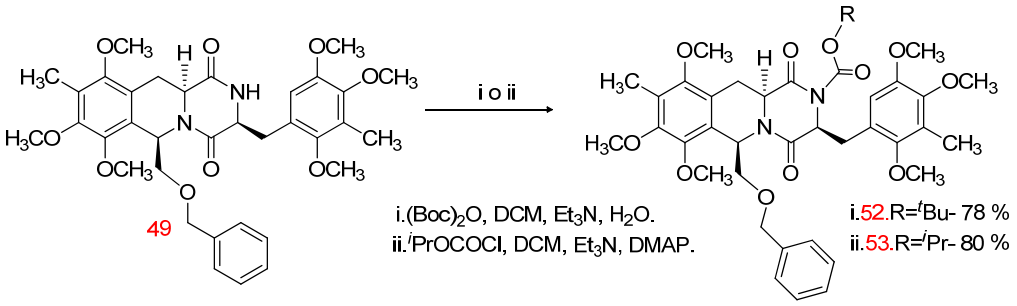
3.3.3.2.2. Formación del enlace carbamato sobre el compuesto 49.

A causa de la nucleofilia del grupo hidroxilo, consideramos conveniente su protección para simplificar el proceso de ciclación. Dado que todos los grupos que han realizado la ciclación del anillo D poseían en C6, como sustituyente, un grupo benciloximetilo, procedimos a su incorporación para investigar si esta sustitución aporta algún beneficio en la ciclación (esquema 3.60).



Esquema 3. 60

A partir de **49** formamos varios carbamatos, con diferente impedimento estérico, para comprobar el efecto de éste sobre la formación del anillo D (esquema 3.61).

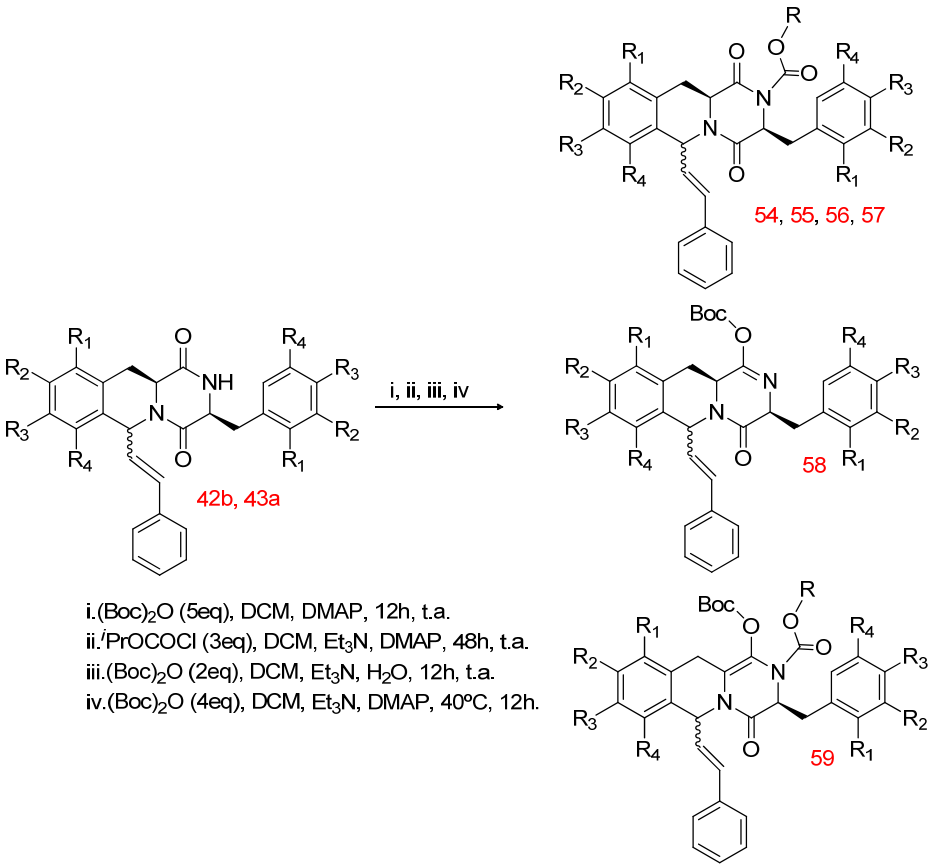


Esquema 3. 61

A pesar de los intentos de seguir la ruta con estas estructuras, todo ensayo realizado para la reducción del carbonilo de C1 falló (tabla 3.14)

3.3.3.2.3. Formación del enlace carbamato sobre los compuestos 42b y 43a.

En este caso, encontramos de nuevo dificultades en la formación de los carbamatos en un medio de reacción básico debido a la acidez del protón H11a (esquema 3.62). Se debe tener muy presente la conservación de la Et_3N en condiciones anhidras, pues la presencia de agua puede tener como resultado la formación de los compuestos indeseados **58** y **59**.



Esquema 3. 62

	Entrada	Condiciones	R	Rdto, %.		
R_1, R_4= -OCH_3 ,R_2,R_3= H	(1)	i	^{t}Bu-	80(54)	18(42b)	-
	(2)	ii	^{i}Pr-	80(56)	16(42b)	-
R_1, R_4, R_3= -OCH_3 ,R_2= CH_3	(3)	i	^{t}Bu-	81(55)	17(43a)	-
	(4)	ii	^{i}Pr-	80(57)	17(43a)	-
	(5)	iii	^{t}Bu-	33(58)	29(55)	26(43a)
	(6)	iv.	^{t}Bu-	22(59)	31(58)	21(43a)

Tabla 3. 13

3.3.3.2.4. Funcionalización de C6 en el compuesto 55.

En un intento de reducción del número de pasos de la secuencia, aplicamos a **55** las condiciones de ruptura oxidativa resumidas en el esquema 3.58. De tener éxito esta

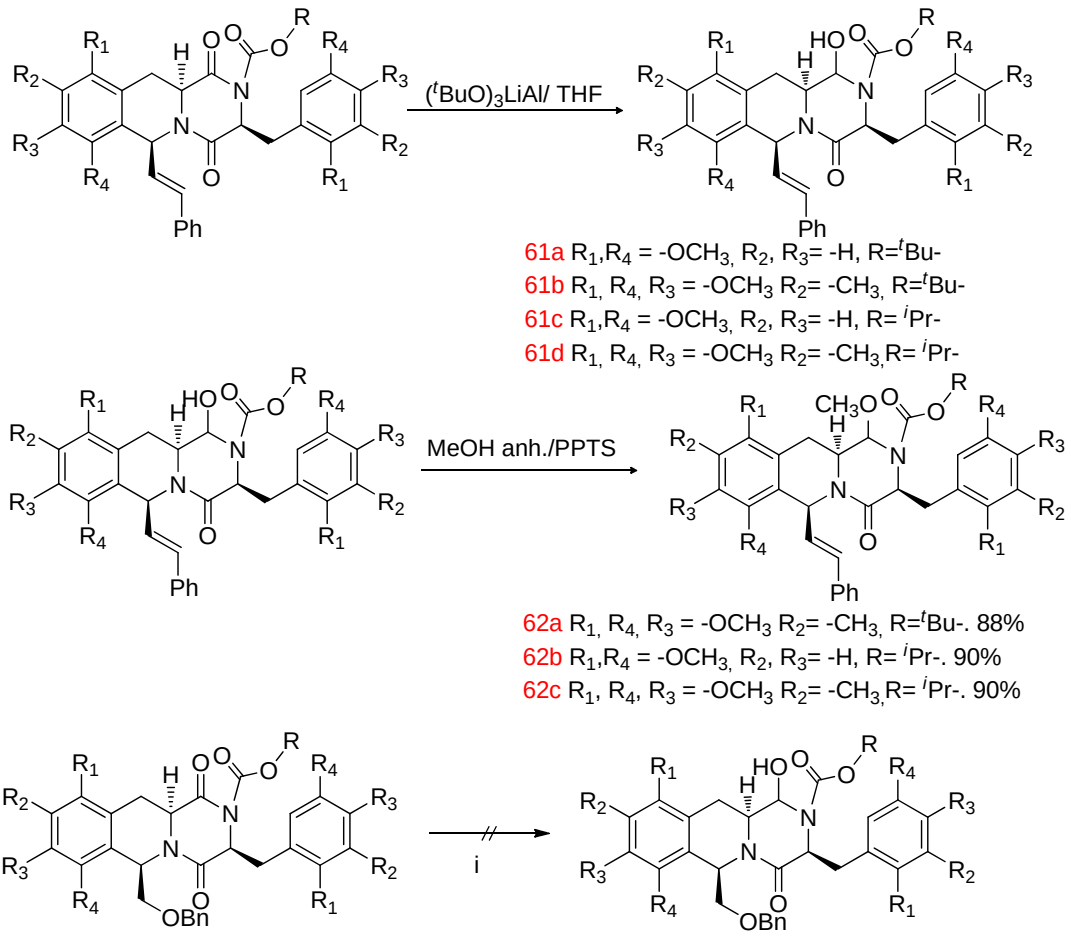
reacción, posibilitaría realizar simultáneamente la reducción del carbonilo en la posición C1 y el aldehído de C6. Sin embargo, el compuesto **60** resultó difícil de caracterizar a causa de la presencia de un elevado número de rotámeros y, sobre todo, demostró una baja estabilidad que nos obligó a reducirlo con tritertbutóxido hidruro de litio y aluminio al alcohol primario correspondiente, pudiendo así generar las dos reducciones en un solo paso (ver el esquema 3.67 más adelante).

Esquema 3. 63

3.3.3.2.5. Generación del hemiaminal en C1.

Una vez activada la posición C1 por incorporación de un grupo aciloxicarbonilo al nitrógeno vecino, el uso de un donador de hidruros impedido debe proporcionar un hemiaminal, que es el sustrato en el que ocurre la reacción de sustitución aromática electrófila que genera el anillo D. Dicho hemiaminal es inestable, lo que en principio impide su aislamiento. En este punto, decidimos ensayar la conversión del grupo C1-hidroxi en otro buen grupo saliente, aunque menos reactivo, como es el metoxilo.[113] Esta transformación se logró por tratamiento de los hemiaminales, en forma de crudos de reacción, con metanol anhidro en presencia de *p*-toluenosulfonato de piridinio (PPTS), como se indica en el esquema 3.64. Tanto los compuestos **61** como **62**, inmediatamente tras su obtención, fueron incorporados a la siguiente reacción para los ensayos de la ciclación del anillo D.

[113](a) Acherki, H.; Álvarez-Ibarra, C.; Guzmán-Fernández, S.; Quiroga-Feijóo, M. L. *Tetrahedron: Asymmetry*, **2004**, *15*, 693. (b) Ortín, I.; González, J. F.; De la Cuesta, E.; Avendaño, *C Tetrahedron*, **2009**, 65, 9944.



61a R_1,R_4 = -OCH_3, R_2, R_3= -H, R=^{t}Bu-
61b R_1, R_4, R_3 = -OCH_3 R_2= -CH_3, R=^{t}Bu-
61c R_1,R_4 = -OCH_3, R_2, R_3= -H, R= ^{i}Pr-
61d R_1, R_4, R_3 = -OCH_3 R_2= -CH_3,R= ^{i}Pr-

62a R_1, R_4, R_3 = -OCH_3 R_2= -CH_3, R=^{t}Bu-. 88%
62b R_1,R_4 = -OCH_3, R_2, R_3= -H, R= ^{i}Pr-. 90%
62c R_1, R_4, R_3 = -OCH_3 R_2= -CH_3,R= ^{i}Pr-. 90%

52 R_1, R_4, R_3 = -OCH_3 R_2= -CH_3, R=^{t}Bu-
53 R_1, R_4, R_3 = -OCH_3 R_2= -CH_3, R= ^{i}Pr-

Esquema 3. 64

Por otro lado, todos los intentos de generar el hemiaminal en los benciloximetil derivados **52** y **53** resultaron fallidos (tabla 3.14).

	Entrada	Compuesto	Condiciones (i)
R_1, R_4, R_3= -OCH_3 ,R_2= CH_3	(1)[114]	53	1) $LiAlH_4$, 1.5 h,-17 ºC, THF anh., 2) 0 ºC, 1 h
	(2)	53	$LiAlH_4$, 2 h, THF anh., t.a.
	(3)	53	$LiAlH_4$, 12 h, THF anh., 30 ºC
	(4)	53	$NaBH_4$ (1.3 eq), -25 ºC, 12 h, AcOH (0.1 eq).
	(5)	53	1) $NaBH_4$ (1.3 eq), -17 ºC, 12 h, AcOH (0.1 eq). 2) 72 h, t.a. 3) $NaBH_4$ (1.3 eq.), 24 h, 50 ºC. 4) $NaBH_4$ (3.9 eq.), 12 h, 85 ºC. 5) $NaBH_4$ (2.3 eq.), 12h, 110 ºC.
	(6)	53	(^{t}BuO)$_3$HLiAl (2.4 eq.), 12 h, t.a, THF anh.
	(7)	52	1) (^{t}BuO)$_3$HLiAl (10 eq.), 48 h, t.a, THF anh. 2) 5 h, 60 ºC.

En todas las reacciones se recupera el compuesto de partida 53 o 52 de forma cuantitativa.

Tabla 3. 14

La inviabilidad de esta reducción se atribuye al impedimento estérico que sufre la posición C1. La disposición de la estructura, en la que la cara superior se encuentra ocupada por el grupo benciloximetileno y la cara inferior por el alcoxicarbonilo correspondiente (figura 3.5), impide la adición del hidruro. Este resultado nos hizo abandonar la vía de acceso al sistema ACEBD mediante el uso de los compuestos **52** y **53**.

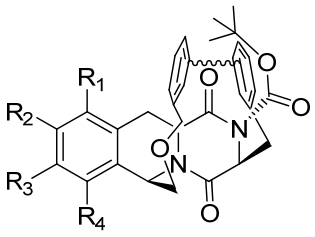
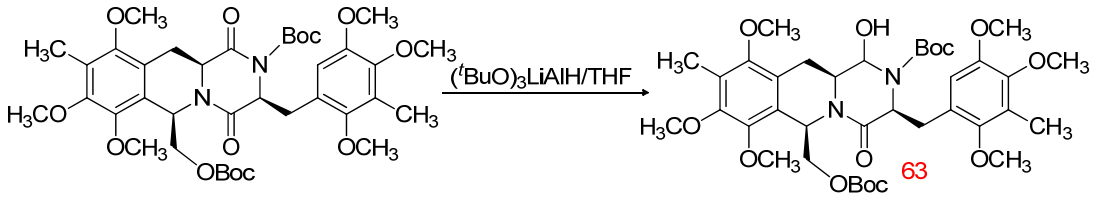


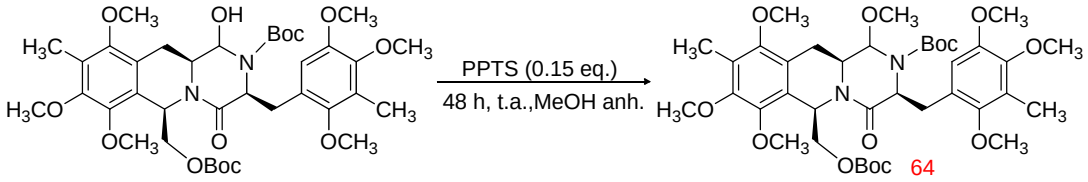
Figura 3. 5

[114] Fukuyama, T.; Linton, S. D.; Tun, M. *Tetrahedron Lett*, **1990,** *31*, 5961.

Las condiciones típicas de reducción, aplicadas al compuesto **50**, rinden la estructura **63**, marcada por la inestabilidad que caracteriza a estos hemiaminales, esto implica como en casos anteriores la inmediata continuación de la secuencia sintética con el compuesto obtenido (esquema 3.65). También en este caso llevamos a cabo la modificación del hemiaminal al correspondiente O-metil derivado (esquema 3.66).

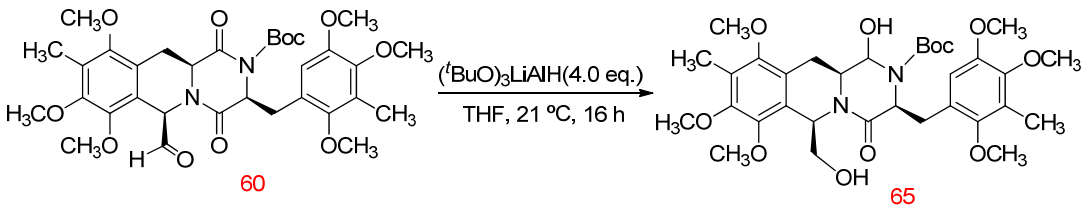


Esquema 3. 65



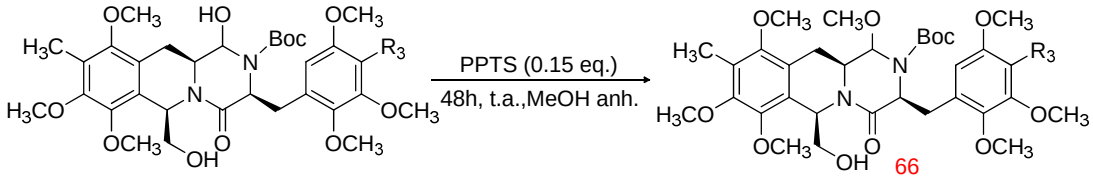
Esquema 3. 66

La reducción doble del compuesto **60** para generar **65** se logró por reacción con un donador de hidruros impedido, como es el tritertbutóxido hidruro de litio y aluminio bajo temperatura controlada (esquema 3.67).



Esquema 3. 67

El compuesto **65**, debido a su inestabilidad, se transformó en **66** (esquema 3.68), que se utilizó inmediatamente como sustrato de reacciones de ciclación para la obtención del anillo D, según se expone en el siguiente apartado (tabla 3.15).

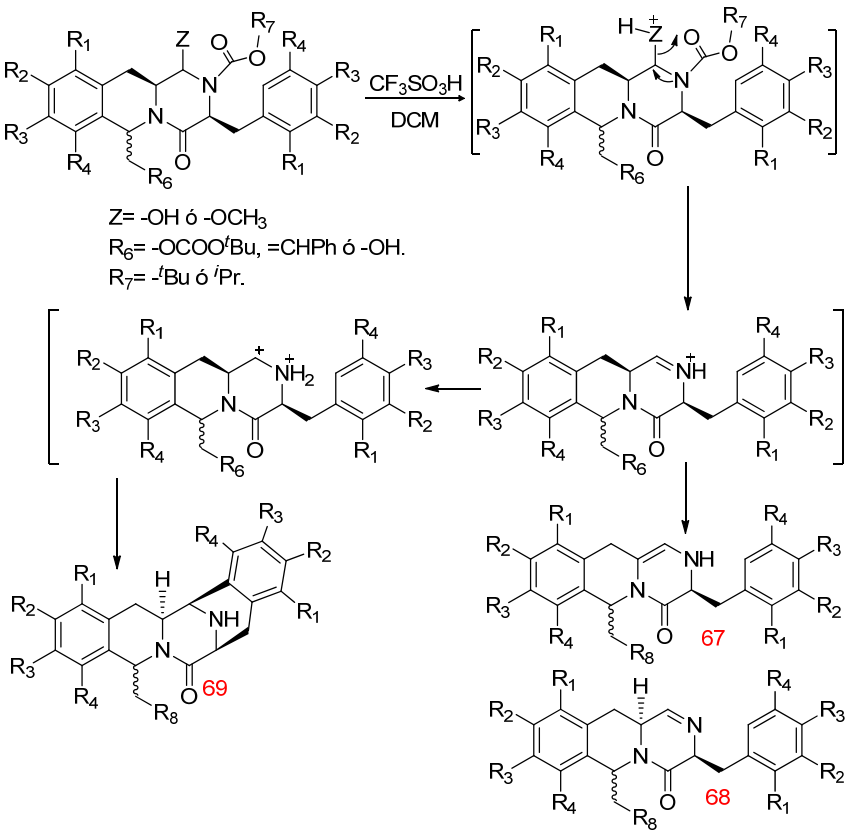


Esquema 3. 68

3.3.3.3. Ciclación del anillo D.

La estrategia basada en la formación del anillo D como último paso para la obtención del núcleo de las saframicinas ha sido seguida por otros grupos de investigación. La opción más habitual, para incrementar la electrofilia de C1 a través de la generación de un catión iminio suele basarse en el empleo de superácidos. Estos ácidos son capaces de proporcionar el dicatión[115] necesario para generar la especie electrófila requerida, mientras que ácidos más débiles nos conducen a las iminas y enaminas correspondientes. En la tabla 3.15 se recogen todas las condiciones aplicadas en la búsqueda de la ciclación del anillo D a partir de los sustratos que se han descrito en el apartado anterior.

[115] Liao, X.W.; Liu, W.; Dong, W.F.; Guan, B.H.; Chen, S.Z.; Liu, Z.Z. *Tetrahedron*, **2009**, 65, 5709.



Esquema 3. 69

	Entrada	Compuesto de partida	Condiciones	R_8	Rdto. %
R_1, R_4= -OCH_3 ,R_2,R_3= H	(1)	**61a**	CF_3SO_3H (20 eq.), 1 h, t.a., DCM anh.	=CHPh	21* (**69a**, *trans*)
	(2)	**61a**	CF_3SO_3H (6.7 eq.), 1 h, t.a., DCM anh.	=CHPh	20* (**68a**, *trans*) 40* (**67a**)
R_1, R_4, R_3= -OCH_3 ,R_2= CH_3	(3)	**63**	CF_3SO_3H (100 eq.), 1 h, 20 ºC, DCM anh.	-OH	50* (**67b**)
	(4)	**63**	CF_3SO_3H (20 eq.), 1.5 h, t.a., DCM anh.	-OH	83* (**67b**)
	(5)	**63**	CF_3SO_3H (100 eq.), 1 h, 60 ºC, DCM anh.	-OH	-----

	(6)	**63**	CF_3SO_3H (10 eq.), 1 h, t.a., DCM anh.	-OH	82* (**67b**)
	(7)	**64**	CF_3SO_3H (19 eq.), 1 h, 20 ºC, DCM anh.	-OH	85* (**67b**)
	(8)	**65**	CF_3SO_3H (20 eq.), 1 h, t.a. DCM anh.	-OH	10# (**67b**)
	(9)	**66**	CF_3SO_3H (50 eq.), 1 h, t.a. DCM anh.	-OH	40# (**67b**)
	(10)	**61d**	CF_3SO_3H (20 eq.), 1 h, t.a. DCM anh.	$CH(OSO_2CF_3)Ph$	21* (**68b**, cis)
	(11)	**61d**	CF_3SO_3H (30 eq.), 1 h, t.a., DCM anh.	$CH(OSO_2CF_3)Ph$	20* (**69b**, cis)
	(12)	**61d**	CF_3SO_3H (40 eq.), 1 h, t.a., DCM anh.	$CH(OSO_2CF_3)Ph$	20* (**68b**, cis)
	(13)	**62b**	CF_3SO_3H (100 eq.), 1 h, t.a.	$CH(OSO_2CF_3)Ph$	10* (**68b**, cis)
	(14)	**61b**	CF_3SO_3H (20 eq.), 1 h, t.a., DCM anh., $MgSO_4$.	$CH(OSO_2CF_3)Ph$	14* (**69b**, *cis*)
	(15)	**61b**	CF_3SO_3H (1.5 eq.), 1.5 h,-10 ºC, DCM anh.	$CH(OSO_2CF_3)Ph$ $CH(OSO_2CF_3)Ph$	21* (**68b**, cis) 11* (**69b**, *cis*)
	(16)	**61b**	CF_3SO_3H (10 eq.), 0.8 h, t.a. DCM anh.	$CH(OSO_2CF_3)Ph$	25* (**69b**, *cis*)
	(17)	**61b**	CF_3SO_3H (20eq.), 1 h, t.a. DCM anh.	$CH(OSO_2CF_3)Ph$	25* (**69b**, *cis*)
	(18)	**61b**	CF_3SO_3H (1.5eq.), 12 h, t.a. DCM anh.	$CH(OSO_2CF_3)Ph$	20* (**69b**, *cis*)
	(19)	**61b**	CF_3SO_3H (1.5eq.), 2 h, -15 ºC, DCM anh.	=CHPh =CHPh	70* (**67c**) 12* (**69c**, *cis*)
R_1, R_4, R_3= -OCH_3 ,R_2= CH_3	(20)	**61b**	CF_3SO_3H (3.0 eq.),H_2SO_4 (10 eq.) 1.5 h, -25 ºC, DCM anh.	----	----
	(21)	**61b**	CF_3SO_3H (40eq.), 1 h, 50 ºC, DCM anh.	----	----
	(22)	**61b**	CF_3SO_3H 75 % en H_2O (49 eq.), 1 h, t.a.	$CH(OSO_2CF_3)Ph$	20* (**69b**, *cis*)
	(23)	**61b**	CF_3SO_3H (20 eq.), 1 h, t.a., DCM anh., tamiz molecular.	$CH(OSO_2CF_3)Ph$	14* (**69b**, *cis*)

	(24)	**62a**	CF_3SO_3H (25 eq.), 1 h, t.a. DCM anh.	$CH(OSO_2CF_3)Ph$	20* (**69b**, *cis*)
	(26)	**62c**	CF_3SO_3H (100 eq.), 1 h, t.a. DCM anh.	----	----

*Rendimientos que implican dos pasos de reacción. #Rendimientos que implican tres pasos de reacción.

Tabla 3. 15

Los datos recogidos en la tabla 3.15 se basan en el empleo del ácido tríflico como agente de protonación para obtener la estructura del pentaciclo. El uso de cualquier otro ácido rinde la correspondientes compuestos **67** y **68**.

La variación en el grupo saliente que se emplea en C1 no influye en la formación del intermedio de iminio y posterior reacción (ciclación o formación de enamina) (entradas 6 y 7, 8 y 9, 17 y 26). De la misma forma la variación en el carbamato tampoco afecta significativamente a la reacción (entradas 11 y 17), e incluso se puede comprobar que las condiciones anhidras no son requisito indispensable para la ciclación (entrada 10 y 22).

Por el contrario, sí se ha encontrado determinante la naturaleza del sustituyente en C9, de forma que la ciclación del anillo D sólo ocurre cuando poseemos un grupo estirilo en esa posición (entradas 16, 17, 18).

Estudiando datos bibliográficos observamos que el único sustituyente presente en la posición C9 de sistemas de saframicina, cuando la ciclación se lleva a cabo por protonación de un hemiaminal, ha sido el benciloximetilo,[116] alcanzándose rendimientos de hasta un 80% del compuesto pentacíclico. Esta observación sugiere que debe existir alguna interacción favorable entre los anillos del sustituyente en C9 y el anillo E. Esto viene apoyado por la disposición que adquiere el compuesto **50** (figura 3.5) donde la imposibilidad de acceder al carbonilo en C1 implica posicionar el grupo benciloxi sobre el carbonilo, muy próximo al anillo E. Debido a este acercamiento entre ambos anillos, sobre la posición de C1, se facilita el ataque nucleófilo del anillo E sobre el catión iminio que se forma, generando rendimientos superiores a los que el sustituyente estiril ofrece.

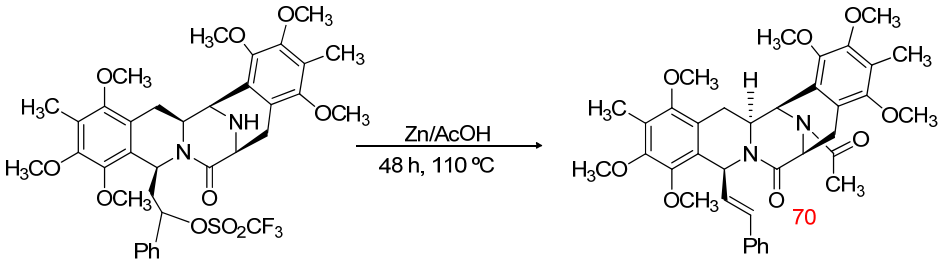
Aun así, el sustituyente estiril también aporta esta interacción, aunque el posicionamiento de ambos anillos debe ser más distante por la rigidez que confiere la insaturación, lo que le conduce a rendimientos moderados en comparación con la imposibilidad de obtener el pentaciclo cuando se aplican otros sustituyentes en C9.

[116](a) Ortín, I.; González, J. F.; De la Cuesta, E.; Avendaño, C. *Tetrahedron* **2009**, *65*, 2201. (b) Liao, X.W.; Liu, W.; Dong, W.F.; Guan, B.H.; Chen, S.Z.; Liu, Z.Z. *Tetrahedron* **2009**, *65*, 5709.

El ácido tríflico tiende a adicionarse a la insaturación del grupo estirilo. Esta reacción no deseada puede evitarse mediante una disminución de la temperatura (entrada 19), pero en ese caso el producto mayoritario es la enamina **69** correspondiente.

3.3.3.4. Reconstrucción del grupo estirilo.

La adición de ácido tríflico a la insaturación exocíclica contenida en el sustituyente C9, por un triflato, imposibilita la aplicación de una ruptura oxidativa como medida para funcionalizar esta cadena. Por ello, ensayamos diversas condiciones para regenerar el grupo estirilo mediante una reacción de eliminación. Como se indica en el esquema 3.70 y en la tabla 3.16, el único método que condujo a la transformación deseada, aunque con rendimiento moderado, consistió en el tratamiento con zinc en ácido acético. La explicación a esta reacción queda recogida en el esquema 3.71.



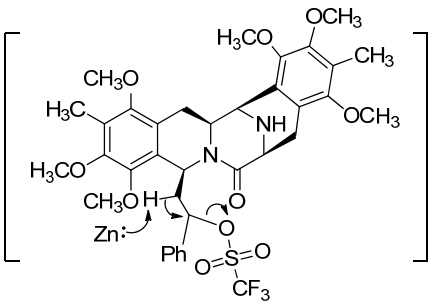
Esquema 3. 70

	Entrada	Condiciones	Rdto. %
R_1, R_4, R_3= -OCH_3 ,R_2= CH_3	(1)	150^{0}C, Xileno	----*
	(2)[117]	MeOH, Et_3N anh.	----*
	(3)	AcOH/H_2SO_4 cat., 65^{0}C	----
	(4)	AcOH/H_2SO_4 cat., t.a.	----*
	(5)	NaH, THF anh., 4h, t.a.	----*
	(6)	Zn/AcOH, 110 ^{0}C, 48h	40(**70**)

*Se recupera producto de partida (**69b**).

[117] Caballero, E.; Avendaño, C.; Menéndez, J. C.; J. Org. Chem., **2003**, *68*, 18.

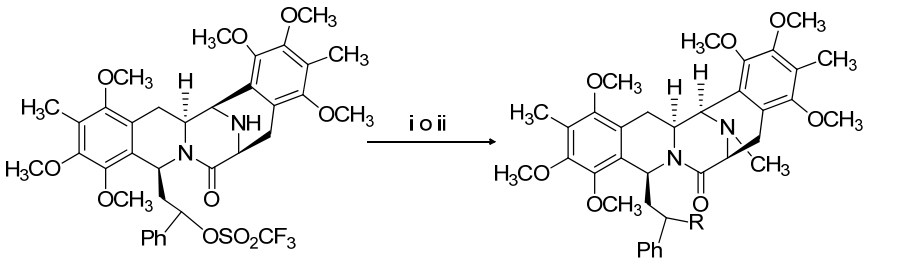
Tabla 3. 16



Esquema 3. 71

3.3.3.5. Derivados N-sustituidos en el sistema pentacíclico.

La metilación del grupo amino es un requisito necesario para alcanzar la sustitución presente en las saframicinas naturales, y se consiguió en las condiciones clásicas de Eschweiler-Clarke (formaldehído-ácido fórmico). En este caso, la donación de hidruro por parte del ácido fórmico da lugar a la hidrogenolisis del grupo triflato a la par que la metilación buscada, generando el análogo **71a** de la saframicina. Alternativamente, la reacción con formaldehído seguida de reducción con cianoborohidruro sódico a temperatura ambiente condujo al compuesto **71b**, con el grupo triflato intacto (esquema 3.72).



i.HCOOH, HCHO,MeOH, reflujo,12h R=- H, 56% 71a.
ii.(a)HCHO, TFA, 2h, t.a.(b)$NaCNBH_3$, 12h R=-OSO_2CF_3 81% 71b.

Esquema 3. 72

3.3.4. Conclusiones.

-Aplicando la ruta sintética ACEBD reducimos el número de pasos de reacción, haciendo uso de los compuestos simétricos **38a** y **38b** como materiales de partida.

-Desarrollamos la ciclación regio y diasteroselectiva necesaria para alcanzar los núcleos de las saframicinas, a través de un intermedio de α-amidosulfona que permite escalar la preparación de intermedios tricíclicos de la ruta sintética.
-Los estudios sobre la ciclación del anillo B en esta ruta sintética, nos permiten comprender las condiciones necesarias para la formación de pirazino[1,2-*b*]isoquinolinas con la estereoquímica requerida (esquema 3.55).
-La posibilidad de funcionalizar la cadena de estirilo, mediante ruptura oxidativa, abre una vía a la obtención de análogos de las saframicinas.
-La acidez que adquiere la posición H11a en la formación del enlace carbamato, en los derivados pirazino[1,2-*b*]isoquinolinas, obliga a un control minucioso de las condiciones para rendir los compuestos deseados.
-Resultó imposible generar el hemiaminal vía reductora, en presencia de un grupo benciloximetilo en C6.
-El uso de superácidos es indispensable para la obtención del anillo D partiendo de hemiaminales,
-La obtención del núcleo de las saframicinas abre la puerta a la aplicación de esta nueva ruta sintética en la construcción rápida de análogos de estos alcaloides.

3.4. Obtención de modificadores de la proteína transmembrana trpm8, nueva diana para el tratamiento del cáncer.

3.4.1. Introducción.

``Los canales iónicos son proteínas responsables de la generación y orquestación de las señales eléctricas que van desde el cerebro, que piensa, hasta el simple músculo que se contrae[118]´´

Con esta definición podemos hacernos una idea del gran abanico de posibilidades que albergan estas proteínas transmembrana, como dianas terapeúticas.

Atendiendo al ión al cuál son permeables, los canales más importantes pertenecen a cuatro grandes grupos: Canales de Na^+, K^+, Ca^{2+} y Cl^-.

Dentro de estos tipos de canales existe una gran diversidad de subtipos, que generalmente realizan una función específica de la célula donde se expresan. Un breve acercamiento a las canalopatías[119] asociadas a mutaciones producidas en los canales voltaje –dependientes nos da una idea de esta diversidad:

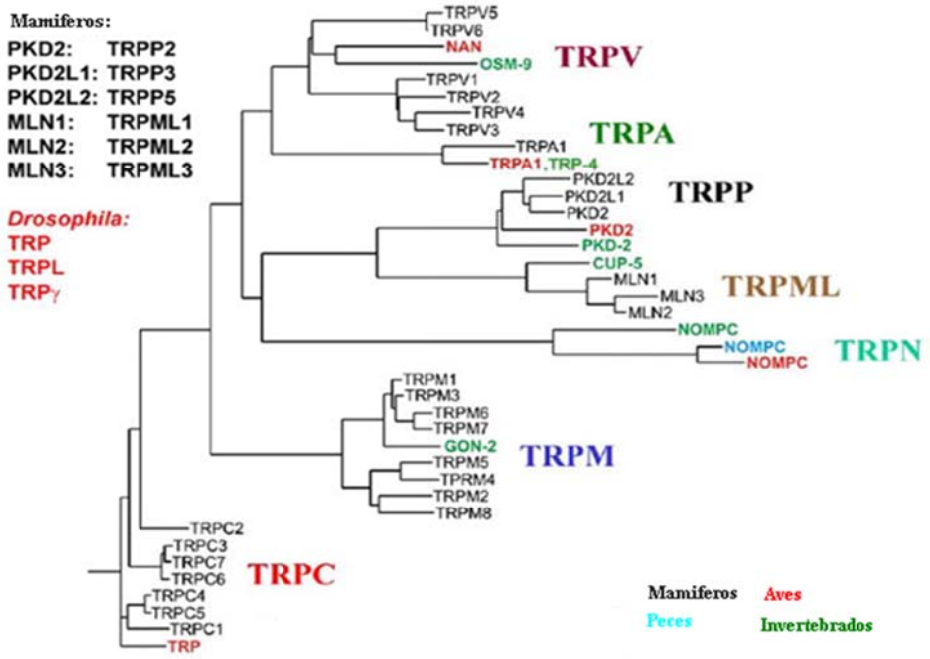
Canal	Subcanal	Enfermedad	Expresión Tisular
Na^+	VD, $Na_v1.1$ α1	Epilepsia con convulsiones febriles	SNC
	VD, $Na_v1.1$ β1	Convulsiones febriles	SNC,corazón, ME
	VD,Na α1	Procesos neurodegenerativos	Corazón, útero, astrocitos
K^+	Kv4.3	Hipertrofia cardiaca	Oído interno, vía auditiva
	Kir1.1-1.3	Síndrome de Bartter	Riñón, páncreas
	KvLQT4	Sordera bilateral	Oído interno, vía auditiva
Ca^{2+}	SK3	Esquizofrenia	Oído interno, vía auditiva
Cl^-	Kir1.1-1.3	Osteopetrosis	Cerebro, testículos, riñón.

Tabla 3. 17

[118] Ackerman, M. J.; Clapham, D. E. *Engl. J. Med.*, **1997**; *336*: 1575.

[119] ``La patología de los canales iónicos (canalopatías): de los canales iónicos a la fisiopatología de la enfermedad.´´ Tamargo Menéndez, J. L., ed. Instituto de España, **2003**.

Encuadrados dentro de los canales permeables a los iones Ca^{2+} y Na^{+}, en 1987[120] se aisló de *Drosophila melanogaster* una familia de proteínas mutadas dependientes del potencial de membrana, que fueron designadas como TRP (*Transient Receptor Potential Channels*) y de los cuales, actualmente se conocen 28 miembros, divididos en 7 subfamilias:



Esquema 3. 73

Todos los receptores TRP son canales catiónicos que permiten el flujo de Ca^{2+} y Na^{+}, aunque según la isoforma implicada, la permeabilidad y la selectividad para cationes mono o divalentes, varía sustancialmente de 100:1 a 0.05:1. Su patrón de distribución tisular es muy amplio, apareciendo expresado en prácticamente todos los tejidos, especialmente en los del sistema nervioso central y periférico, en los que desempeñan un papel crucial en la transducción sensorial, convirtiendo los estímulos ambientales en cambios de excitabilidad de la membrana neuronal.

[120] Kamb, A.; Iverson, L. E.; Tanouye, M. A. **1987**,*Cell* 50, 405.(b)Papazian, D. M.; Schwarz, T. L.; Tempel, B. L.; Jan, Y. N.; Jan, L. Y.,*Science* **1987,** *237, 749.* (c) Venkatachalan, K.; Montell, *Annu. Rev. Biochem* **2007**. 76, 387.

Existen dos canales pertenecientes a la familia de las TRP que reciben la denominación de termo-dependientes por activarse a diferentes temperaturas: TRPV1 (receptor de calor)[121] y TRPM8 (receptor de frío)[122].

El cDNA, del canal TRPM8, fue clonado por primera vez, durante un estudio de cáncer de próstata[123]. Posteriores investigaciones en canales TRPM8 de ratas y ratones, realizadas por dos grupos de investigación distintos, clasificaron a este canal como termo-dependiente y cooling agent-dependiente[124]. Se encontró que este canal iónico se activaba a temperaturas comprendidas entre 10–28 ºC a la vez que también resultaba activado por agentes químicos que poseían la propiedad de transmitir la sensación de frío como el mentol y eucaliptol (cooling agent) y también por icilin (super-cooling agent), éste último en presencia de Ca^{2+} extracelular[125] , lo que implica una variación en el potencial de membrana.
De entre todas las subfamilias existentes nos centraremos en la TRPM8 (*Transient Receptor Potential Melastatin*) cuya sobreexpresión en células cancerígenas de mama, colon, recto y próstata ha sido documentada recientemente. Especialmente ha sido estudiada la sobreexpresión de TRPM8 en las células epiteliales de próstata, donde se ha comprobado la hormono dependencia de estos canales. El hecho de que el canal TRPM8 se encuentre altamente expresado en tejidos tumorales en comparación con los sanos proporciona la posibilidad de tratar estos canales como una diana en el desarrollo de fármacos.

3.4.2. Morfología del canal TRPM8.

Teniendo en cuenta que los estudios sobre este canal son bastante recientes es comprensible que el conocimiento sobre su funcionamiento diste mucho de ser completo.
Este canal está constituido por seis dominios transmembrana (TM; S1-S6) y un poro (P) que se encuentra entre S5 y S6. Dentro de los seis dominios transmembrana es importante destacar el sensor de voltaje (intracelular), y el extremo C-terminal (figura 3.6).

[121] (a) Caterina, M.J.; Schumacher, M.A.; Tominaga, M.; Rosen, T.A. ; Levine, J.D.; Julius, D. *Nature*, **1997**, *389,* 816.(b) Jordt, S.; Julius, D. *Cell*, **2002** , *108*, 421.
[122] Peier, A.M.; Moqrich, A.; Hergarden, A.; Reeve, A.; Andersson, D.; Story, G.; Earley, T.; Dragoni, I.; McIntyre, P.; Bevan, S.; Patapoutian, A., *Cell,* **2002**, *108,* 705.
[123]Tsavaler, L.; Shapero, M.H.; Morkowski, S.; Laus,R.; *Cancer Res*, **2001**, *61*, 3760.
[124](a)McKemy, D.; Neuhausser, W.; Julius, D.; *Nature*, **2002**, 416, 52.(b) Peier, A.M.; Moqrich, A.; Hergarden, A.; Reeve, A.; Andersson, D.; Story, G.; Earley, T.; Dragoni, I.; McIntyre, P.; Bevan, S.; Patapoutian, A. *Cell*, **2002**, *108*, 705.
[125] Chuang, H.; Neuhausser, W.N.; Julius D, *Neuron,* **2004**, *43,* 859.

3.4.2.1. Sensor de voltaje.

El TRPM8 está clasificado como un canal dependiente del voltaje. Una parte del dominio S4 que se conserva en toda la familia TRPM es un residuo de arginina y además TRPM8 contiene un residuo de histidina que puede ser cargado positivamente dependiendo del pKa del medio. Voets *et. al.*[126] (figura 3.6) en su estudio sobre estos canales concluyó que la neutralización de las cargas contenidas en S4, R842 y K856 ,en la unión entre S4-S5, reduce la dependencia de los poros al potencial lo que indica que estos dominios son parte del sensor de voltaje. Más tarde, Latorre *et. al.*[127] apuntaron la imposibilidad de que esas cargas contribuyesen a la totalidad del efecto de apertura-cierre del poro proponiendo un módulo de sensor mayor, incorporando el fragmento que comienza en la lisina 856 hasta la totalidad del sitio de unión entre S4-S5.
El residuo Y745 localizado en S2 se ve fuertemente afectado por la concentración de mentol lo que lo define como un sitio de unión con el canal[128]. Mutaciones en S4 (R842H) afectan a la actividad del mentol esto sugiere una interacción con el bolsillo hidrofóbico incluido entre los dominios S2 y S4[129].
Por otro lado, los residuos implicados en el reconocimiento del icilin se encuentran situados en S3, N799, D802, y G805 (en TRPM8 de ratas), lo que implica que los sitios de unión del mentol y del icilin no se superponen y por lo tanto la activación del canal transcurre por mecanismos distintos[130]. El icilin, clasificado como un *super-cooling agent*, posee una estructura química que no guarda similitud alguna con el mentol, clasificado como *cooling agent*, poseyendo un efecto 200 veces superior al mentol, aunque para alcanzar esta máxima eficacia requiere de una elevación del Ca^{2+} intracelular.

3.4.2.2. Módulo del poro.

TRPM8 es un canal no-selectivo, aunque existe una cierta discriminación frente a los cationes monovalentes y una alta permeabilidad hacia los iones calcio[131].
La región localizada en el lazo S5-S6 (figura 3.6) se mantiene en todos los miembros de la familia TRP y con alta conservación de la parte hidrofóbica, presente al comienzo de la región del poro, desde Y908 a Y912 y un aspartato invariable en posición 920[132]. La neutralización de D920 en TRPM8 conduce a la inactividad del canal. Por otro lado la

[126] T. Voets, G. Owsianik, A. Janssens, K. Talavera, B. Nilius, *Nat. Chem. Biol*., **2007**, *3,* 35.
[127] Latorre,R.; Brauchi S.; Orta, G.; Zaelzer, c.; Vargas, G. *Cell Calcium,* **2007**, *42,* 427.
[128] M. Bandell, A. Dubin, M. Petrus, A. Orth, J. Mathur, S. Hwang, A. Patapoutian, *Nat. Neurosci*., **2006**, *9*, 466.
[129] T. Voets, G. Owsianik, A. Janssens, K. Talavera, B. Nilius, *Nat. Chem. Biol*., **2007**, *3*, 35.
[130] Chuang, H.; Neuhausser, W.N.; Julius D. *Neuron,* **2004,** *43*, 859.
[131] McKemy, D.; Neuhausser, W.; Julius, D. *Nature*, **2002,** *416*, 52.
[132] (a).-L. Perraud, C. Schmitz, A. Scharenberg, *Cell Calcium*, **2003**, *33*, 519.(b) C.N.Topala,W.T. Groenestege, S. Th´ebault, D.Van den Berg, B. Nilius, J.G. Hoenderop, R.J. Bindels, *Cell Calcium*, **2007**, *41*, 513.

sustitución de Q914 por glutamato altera la permeabilidad a cationes monovalentes y genera una moderada permeabilidad al Ca^{2+}[133].

Se ha identificada una posición de glicosidación en N934[134]. Este sitio contiene un residuo de dos cisteínas (C929 y C940) las cuales son esenciales para el correcto funcionamiento del canal.

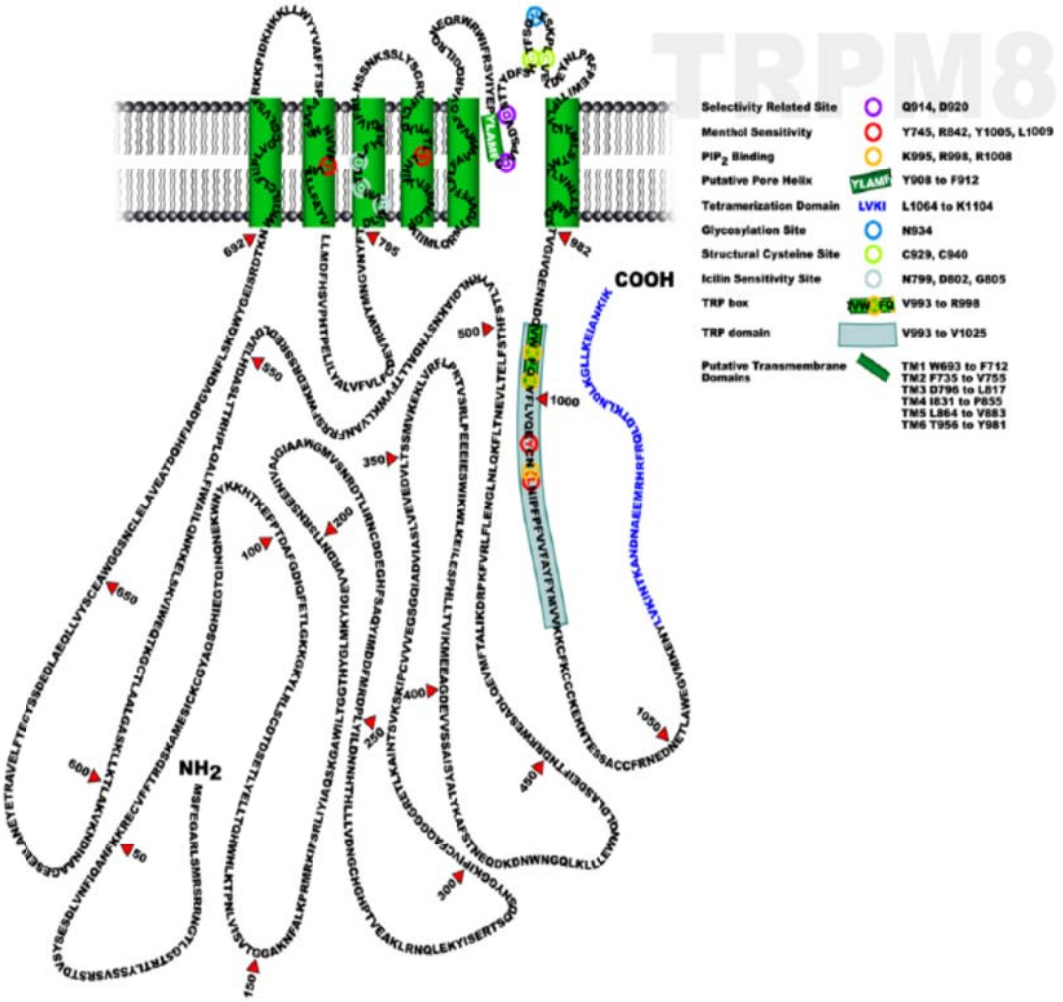


Figura 3. 6

[133] B. Nilius, J. Prenen, A. Janssens, G. Owsianik, C. Wang, M. Zhu, T. Voets, *J. Biol. Chem*., **2005,** *280*, 22899.

[134] (a)I. Dragoni, E. Guida, P. McIntyre, *J.Biol. Chem*., **2006**, *281*, 37353. (b) I. Erler, D.M. Al-Ansary, U. Wissenbach, T.F. Wagner, V. Flockerzi, B.A. Niemeyer, *J. Biol. Chem*., **2006**, *281*, 38396.

3.4.2.3. Módulo C-terminal.

Este módulo está constituido por una TRP-box que se conserva en todos los miembros de esta familia (VWKFQR) y un dominio TRP (figura 3.6).
Los residuos K995, R998 y R1008 en el dominio TRP están directamente relacionados en la activación de TRPM8 a través de PIP_2[135]. La hidrólisis del fosfatidilinositol-4,5-bisfosfato, marcado por un incremento en el Ca^{2+} del citosol, pone en marcha una cascada de señales que se traduce en una desensibilización del canal.
El Y1005 y L1009, localizados en el dominio TRP, están implicados en la activación de TRPM8 por mentol[136], aunque una serie de mutaciones en el canal muestran un mecanismo de apertura distinto para la activación por mentol del proveniente de la temperatura, voltaje o PIP_2[137].A demás, aunque todavía existe controversia al respecto, recientemente se ha propuesto que el voltaje y la temperatura interaccionan alostéricamente, empleando la idea de un módulo del canal sensible al voltaje y otro modulo diferente que resulta activado por la temperatura.

3.4.3. Mecanismo de acción.

Básicamente y de forma resumida, atendiendo a la apertura y cierre de este canal mediante el voltaje, podemos observar (figura 3.7) que la entrada de cargas positivas al citosol genera una despolarización de la membrana (se igualan las cargas extracelulares he intracelulares), lo que induce a un primer paso en el cierre del poro por cambios en la conformación de la proteína. Por otro lado, al aumentar la carga positiva en el citosol se genera una serie de respuestas en cascada. El efecto de repulsión sobre las cargas positivas contenidas en la parte intracelular de la proteína (unión entre S4-S5 donde está localizado el sensor de voltaje), esta repulsión produce un movimiento en la parte de la proteína que constituye el poro, cerrando éste. Al mismo tiempo, los cationes presentes liberan la PLC (fosfolipasa C, posiblemente la PLCγ1) hidrolizando el fosfatidilinositol 4,5-bifosfato (PIP2). Esto se traduce en una ruptura de la interacción con el dominio carboxílico terminal de la TRPM8 que mantenía el canal abierto, generando inositol 1,4,5 trifosfato (IP3) y diacilglicerol (DAG), así como la inactivación del canal[138].

[135] T. Roh´acs, C.M. Lopes, I. Michailidis, D.E. Logothetis, *Nat. Neurosci.*, **2005**, *8*, 626.
[136] M. Bandell, A. Dubin, M. Petrus, A. Orth, J. Mathur, S. Hwang, A. Patapoutian, , *Nat. Neurosci.*, **2006**, *9,* 466.
[137] D.A. Andersson, H.W. Chase, S. Bevan, *J.Neurosci.*, **2004**, *24*, 5364.
[138] *Zhang, L. Barritt*, G. J. *Endocrine-Related Cancer,* **2001**, *13,* 27.

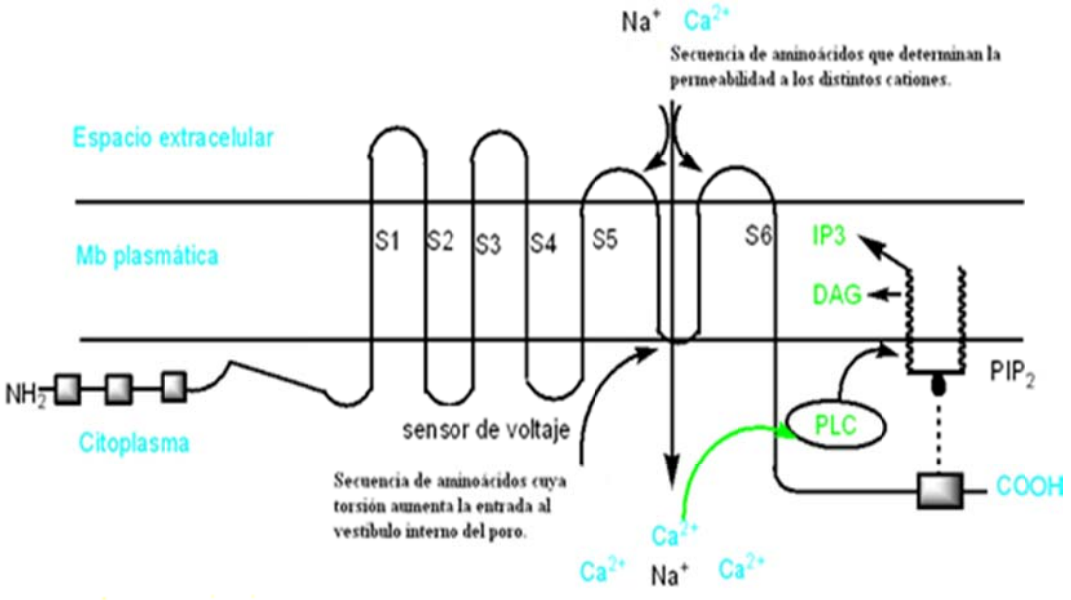
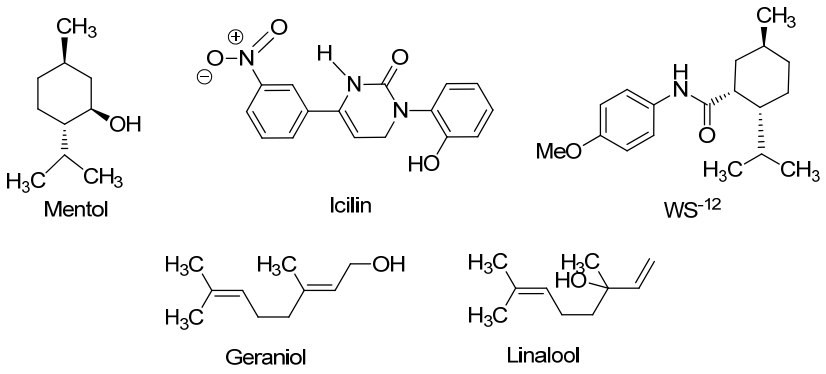


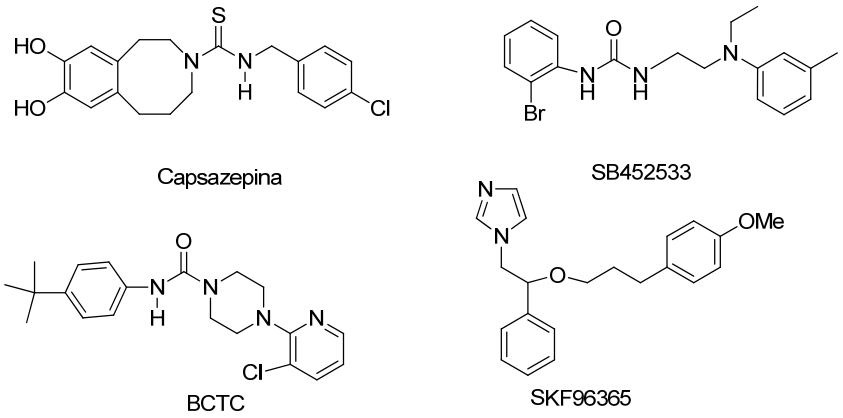
Figura 3. 7

3.4.4. Agonistas y antagonistas. Mecanismo de implicación en el tratamiento del cáncer.

La temperatura (entre 10 y 28 ºC) y agentes químicos (mentol e icilin) han quedado establecidas como agonistas de estas estructuras proteicas. Aunque su número va en aumento, debido a las recientes investigaciones realizadas podemos incluir como agonistas adicionales la mentona, eucaliptol, geraniol, linalool y WS-12 (esquema 3.74). También han sido encontradas sustancias antagonistas como capsazepina (antagonista del efecto del mentol) o el BTCT, el tiol del BTCT, SB-452533, SKF96365 (esquema 3.75)[138].



Esquema 3. 74



Esquema 3. 75

Químicamente se puede observar la disparidad entre sus funciones en relación a su actividad como agonistas o antagonistas aunque ciertamente la función amida parece verse envuelta en ambos procesos.

Como ya se expuso en apartados anteriores, la sobreexpresión de este canal en células cancerígenas, con respecto a las células sanas, hacen de este canal una diana terapéutica en estudio. Una aplicación más reciente enmarca este canal con fines de diagnóstico, ya que la alta afinidad de estructuras químicas pertenecientes al grupo de los ``*super-cooling agents´´* y la posibilidad de introducir isótopos radiactivos en la estructura (^{18}F) permite el uso de técnicas de radiodiagnóstico[139](PET).

[139] Benjamin Beck, B.; Bidaux, G.; Bavencoffe, A.; Lemonnier, L.; Thebault, S.; Shuba, Y.; Barrit G.; Skryma, R.; Prevarskaya, N.; *Cell Calcium,* **2007,** *41,* 285.

El mecanismo de necrosis está ligado a la concentración de Ca^{2+} intracelular, pero también al estadío del desarrollo celular. El incremento de los niveles de Ca^{2+} en el retículo endoplasmático genera una resistencia a la apoptosis en las células neoplásicas tardías. Por el contrario, cuando se produce una variación en los niveles de Ca^{2+} en células neoplásicas tempranas, éstas tienden a la apoptosis fácilmente[138]. Es por ello que podemos encontrar casos en los que tanto agonistas como antagonistas induzcan una apoptosis[140] en células cancerígenas donde se encuentra sobreexpresado el canal TRPM8.
Aunque se ha encontrado sobreexpresión de TRPM8 en tejidos tumorales de próstata, pulmón, colorectal, pecho y melanoma,[141] la única línea celular en la que ha sido aplicado el estudio pertenece a la LNCaP, es una línea celular de próstata hormono-dependiente. El canal TRPM8 es hormono-dependiente, por lo que su expresión viene regulada por la presencia de andrógenos en LNCaP. Por el contrario, se ha demostrado que líneas celulares hormono-independientes (PC3) no presentan una sobreexpresión del canal[142].

3.4.5. Síntesis de modificadores del canal TRPM8.

3.4.5.1. Antecedentes.

Existen varias patentes en las que describen estudios sobre el efecto agonista de benziloxifenilamidas y sus carbamatos[143] y derivados de benzotiofeno y benzofurano[144] sobre el canal TRPM8 en el tratamiento de enfermedades respiratorias y urológicas. También se han estudiado antagonistas y agonistas derivados de estructuras de *p*-mentano sustituido en la posición 3 como inductores de la apoptosis en células con una sobreexpresión del canal TRPM8[145] (figura 3.8).

[140] Ortar, G.; De Petrocellis, L.; Morera, L.; Schiano Moriello, A.; Orlando, P.; Morera ,E.; Nalli , M.; Di Marzo, V. *Bioorganic & Medicinal Chemistry Letters*, **2010**, *20,* 2729.
[141] Larisa Tsavaler, L.; Shapero, M. H.; Morkowski, S.; Laus, R.; *Cancer Res,* **2001**; *61*, 3760.
[142] Zhang. L. and Gregory John Barritt, G. *Cancer Research,* **2004**, *64*, 8365.
[143] (a) Lampe, T.; Alonso-Alija, C.; Beck, H.; Rosentreter, U.; Sandner, P.; Stahl, E.; Stelte-Ludwig, B. PCT Int. Appl. WO2007017094, **2007**. (b) Lampe, T.; Alonso-Alija, C.; Beck, H.; Rosentreter, U.; Sandner, P.; Stahl, E.; Stelte-Ludwig, B. PCT Int. Appl. WO2007017093, **2007**.; (c) Lampe, T.; Alonso-Alija, C.; Bauser, M.;Beck, H.; Rosentreter, U.; Sandner, P.; Stahl, E.; Stelte-Ludwig, B. PCT Int. Appl.WO2007017092, **2007**.; (d) Lampe, T.; Alonso-Alija, C.; Stelte-Ludwig, B.; Sandner, P.; Bauser, M.; Beck, H.; Lustig, K.; Rosentreter, U.; Stahl, E.; Takagi, H.PCT Int. Appl. WO2006040136, **2006**.
[144] Colburn, R. W.; Dax, S. L.; Flores, C.; Matthews, J.; Qin, N.; Youngman, M. A.; Teleha, C.; Reany, L. PCT Int. Appl. WO2007134107, **2007**.
[145] Ortar, G.; De Petrocellis, L.; Morera, L.; Schiano Moriello, A.; Orlando, P.; Morera ,E.; Nalli , M.; Di Marzo, V.*Bioorganic & Medicinal Chemistry Letters*, **2010**, *20,* 2729.

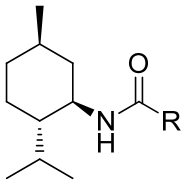
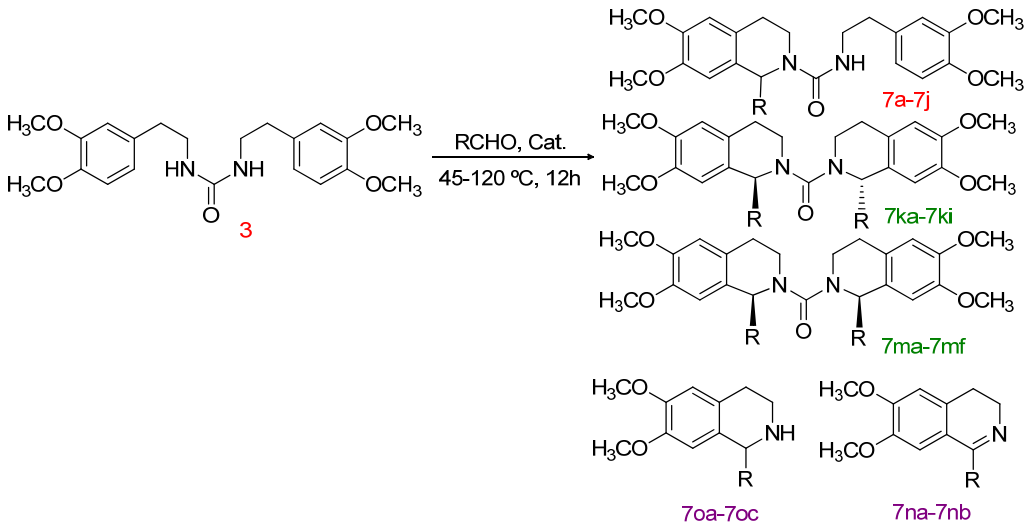


Figura 3. 8

3.4.5.2. Síntesis de bisisoquinolina metanonas e isoquinolina carboxamidas

En vista de que la función urea está presente en algunos de los compuestos que poseen actividad sobre estos canales, decidimos síntetizar estructuras que contuvieran el núcleo tetrahidroisoquinolínico y una función urea. Para ello partiremos de las difenetilureas obtenidas a partir de la homoveratrilamina (esquema 3.5). Como ya se expuso al comienzo del estudio de la síntesis de THiQ, a partir del compuesto **3** es posible alcanzar las estructuras cicladas mediante el uso de aldehídos a través de intermedios α-amidosulfona (serie **7**, tabla 3.1). Aplicar estas condiciones a varios aldehídos nos ha conducido a la serie de compuestos reflejados en la tabla 3.18 y el esquema 3.76.



Esquema 3. 76

R	T(°C)	Cat	Solv.	Monocicla %	Dicicla %	Ratio R*R*/ R*S*	Comp.
p-Br-C_6H_4-	45	$TolSO_2H$	DCM	40	-		7a
	80	$TolSO_2H$	AcOEt	75	25	1/0	7a/7ke
	80	$TolSO_2H$	Toluene	60	-		7a
	120	$TolSO_2H$	Toluene	54	41	1/0	7a/7ke
m-NO_2-C_6H_4-	45	$TolSO_2H$	DCM	50	-		7b
	80	$TolSO_2H$	AcOEt	85	15	1/0	7b/7kc
	120	$TolSO_2H$	Toluene	-	82	1/0	7kc
p-Cl-C_6H_4-	45	$TolSO_2H$	DCM	56	-		7c
	80	$TolSO_2H$	AcOEt	85	-		7c
	80	$TolSO_2H$	Toluene	-	34	1/0	7kf
	120	$TolSO_2H$	Toluene	-	37	1/0	7kf/7oc(34%)
Ph-	45	$TolSO_2H$	DCM	49	-		7d
	80	$TolSO_2H$	AcOEt	46	-		7d
	*80	$TolSO_2H$	AcOEt	53	41	1/0	7d/7kd
	120	$TolSO_2H$	Toluene	-	73	1/0	7kd
CH_3CH_2	45	$TolSO_2H$	DCM	60	32	0/1	7g/7md
	45	$TolSO_2H$	Toluene	64	-		7e
$EtCH_2$	45	$TolSO_2H$	DCM	58	-		7f
	80	$TolSO_2H$	AcOEt	52	-		7f
	80	$TolSO_2H$	Toluene	45	-		7f
	120	$TolSO_2H$	Toluene	-	60	0/1	7me
o-Cl-C_6H_4-	45	$TolSO_2H$	DCM	53	-		7h
	80	$TolSO_2H$	AcOEt	53	-		7h
	120	$TolSO_2H$	Toluene	-	40	0/1	7mf
o,p-NO_2-C_6H_4-	80	H_2SO_4	AcOH	50	20	0/1	7i/7mb
	120	$TolSO_2H$	Toluene	-	-		7oa (16%)
p-NO_2-C_6H_4-	80	$TolSO_2H$	AcOEt	25	-		7j
	80	H_2SO_4	AcOH	20	50	1/0	7j/7kh
	120	$TolSO_2H$	Toluene	-	50	1/0	7kh
p-F- C_6H_4-	65	H_2SO_4	AcOH	-	30/4	1/0.15	7ka/7ma
	80	H_2SO_4	AcOH	-	17	0/1	7ma
	120	H_2SO_4	AcOH	-	37	0/1	7ma
	120	$TolSO_2H$	Toluene	-	30	1/0	7ka
p-NO_2-C_6H_4-O-C_6H_4-	80	$TolSO_2H$	Toluene	-	21	1/0	7kb
	120	H_2SO_4	AcOH	-	36	0/1	7mc
2-Naftil-	120	$TolSO_2H$	Toluene	-	40	1/0	7kg
3(m-NO_2-C_6H_4-)piridin-2-il	80	H_2SO_4	AcOH	-	66	1/0	7ki
	120	H_2SO_4	AcOH	-	-		7nb(20%)/7ob(38 %)

dihidroqu	80	H_2SO_4	AcOH	-	-	7na(99%)
inolin-2-il	120	H_2SO_4	AcOH	-	-	7na(81%)

* 72 h de reacción

Tabla 3. 18

El empleo de $TolSO_2H$ como catalizador de la reacción a distintas temperaturas nos permite controlar la regioselectividad del proceso. Con temperaturas inferiores a 80 ºC se alcanzan los compuestos monociclados (**7a**-**7j**) mientras que temperaturas de 120 ºC conducen a los compuestos diciclados con una disposición relativa *trans* entre los sustituyentes de C1 de ambas tetrahidroisoquinolinas cuando los aldehídos empleados son aromáticos (**7ka**-**7ki**), y *cis* cuando se trata de sustituyentes alifáticos (**7md**-**7me**).

Del estudio del efecto de los sustituyentes en los aldehídos aromáticos de partida se puede deducir que:

- en la posición *para*, la naturaleza electronegativa de los halógenos no influye en la ciclación del compuesto final. Así **7a** y **7c**, a 45 ºC, dan el mismo rendimiento sobre la monociclación y **7kf**, **7ka** a 120ºC no varían en el rendimiento en la diciclación.
- en posición *orto*, el impedimento estérico produce una disminución en el rendimiento de la reacción. Comparando **7h** (aldehído con sustituyente cloro en *orto*) y **7c** (aldehído con sustituyente cloro en *para*) a 80 ºC se observa el incremento en el rendimiento de **7c**.

Por otro lado, cuando el catalizador usado es H_2SO_4 (la ciclación transcurre por un intermedio de oxonio) se aprecia la falta de diasteroselectividad en la reacción (**7ma**), aunque este método produce la ciclación de estructuras que no son posibles obtener mediante la aplicación del intermedio de α-amidosulfona (**7i**, **7mb**, **7ki**).

Aunque los rendimientos resultan bajos en muchos casos, cuando usamos el intermedio de α-amidosulfona, se previene la hidrólisis que generan las condiciones ácidas del método de ciclación clásico, además de ofrecernos una diastero- y regioselección controlable por el efecto de la temperatura.

Con estos resultados experimentales podemos concluir que los intermedios con gran volumen generan repulsiones estéricas entre sí, las cuales conducen a los compuestos *trans* (*R***R**), es el caso de los sustituyentes aromáticos en el intermedio de α-amidosulfonas o la reacción clásica de Pictet Spengler en aldehídos extremadamente voluminosos (**7kg** y **7ki**). Mientras que cuando el intermedio es generado sobre un aldehído alifático, los intermedios de α-amidosulfonas conducen a intermedios que poseen menor impedimento estérico con

lo que la disposición adquirida es *cis*. Esto mismo ocurre con la reacción clásica de Pictet-Spengler en aldehídos aromáticos de moderado volumen (**7ma**).

3.4.6. Estudio de relación estructura-actividad (SAR).

Los compuestos portadores de la función urea y algunos ejemplos representativos de las series que contienen el núcleo de piperazinodionas, fueron ensayados biológicamente, para ser clasificados como agonistas o antagonistas del canal TRPM8 (tabla 3.21) [146].

Compuesto (R=sustituyente C1)	Potency EC_{50} TRPM8 µM	IC_{50} inhibition (desensibilization) TRPM8 µM (icilin 0.25 µM)
3	53.6	**> 100**
7g	48.5	**39.8**
7a (R=*p*-Br-C_6H_4)	NA	**> 100**
7b (R=*m*-NO2- C_6H_4)	13.5	**> 100**
7c (R=*p*-Cl- C_6H_4)	1.3	**> 100**
7d (R=Ph-)	27.4	**2.4 ± 0.6**
7e (R=CH_3CH_2)	15.25	**72.4**
7f (R=$EtCH_2$)	10.9	**> 100**
7h (R=*o*-Cl- C_6H_4)	11.6	**40.0**
7ka (R=*p*-F- C_6H_4)	NA	**0.11 ± 0.01**
7kc (R=*m*-NO2- C_6H_4)	20.5	**23.4**
7kd (R=Ph)	17.0	**0.85± 0.04**
7ke (R=*p*-Br-C_6H_4)	71.0	**4.8 ± 1.8**
7kf (R=*p*-Cl- C_6H_4)	5.9	**0.54± 0.13**
7kg (R=2-Naftil)	NA	**17.6 ± 1.4**
7kh (R= *p*-NO_2- C_6H_4)	11.3	**44.2 ± 5.9**
7ki (R= 3(m-NO2- C_6H_4-)piridin-2-il)	NA	**19.1 ± 1.8**
7ma (R= *p*-F- C_6H_4)	NA	**> 100**
7mb (R= *o,m*-NO2- C_6H_4-)	NA	**36.9 ± 4.1**
7me (R= $EtCH_2$)	57.2	**11.8 ± 2.3**

[146] Este estudio fue realizado por el grupo del Dr. Luciano De Petrocellis *et. al*, en la Universidad de Nápoles.

7mf (R= *o*-Cl- C_6H_4)	9.9	**11.3 ± 0.9**
7na (R=dihidroquinolin-2-il)	NA	**50.1 ± 0.4**
7nb (R= 3(*m*-NO2- C_6H_4-)piridin-2-il)	NA	**52.5 ± 17.9**
7oa (R= *o,m*-NO2- C_6H_4)	NA	**> 100**
7oc (R= *p*-Cl- C_6H_4)	NA	**67.1 ± 7.6**
21c	15.9 ± 0.1	**11.8 ± 1.0**
21d	NA	**23.0 ± 1.2**
21e	NA	**20.6 ± 0.3**
21f	NA	**24.7 ± 0.5**
21n	19.1	**0.65± 0.06**
38b	-	**> 100**
42b	-	**14.5± 0.04**
43a	14.1	**3.1 ± 0.1**
45	**5.0**	**9.5± 2.9**

Tabla 3. 19

Del estudio realizado sobre los compuestos que presentan la función urea, podemos concluir que poseen un efecto antagonista sobre los canales TRPM8 ya que el IC_{50} (concentración necesaria del compuesto para producir una inhibición del 50%) en presencia de un superagonista como es el icilin, muestra valores del orden μM, lo que convierte a estos compuestos en potentes antagonistas de estos receptores (**7d**, **7kf**, **7ke**, **7kd**, **7ka**). Algunos compuestos presentan un carácter también agonista, EC_{50}, incrementándose el poder agonista con la disminución en el valor de la concentración.

Del estudio SAR realizado podemos deducir que tanto la presencia del anillo de tetrahidroisoquinolina, como la función urea son necesarias para proporcionar propiedades antagonistas de TRPM8 a estos compuestos. El compuesto **3** no presenta actividad poseyendo sólo la función urea, así como los compuestos **7oa**, **7ab** conteniendo solamente la estructura tetrahidroisquinolina tampoco tienen efecto sobre el canal.

Por otro lado, la presencia de los dos ciclos de THiQ produce una mayor actividad con respecto a las estructuras de un solo anillo de THiQ (compuesto **7d** Vs **7kd**).

Los sustituyentes de naturaleza arílica en el C1 de las THiQ son más eficientes que los alquilos (compuesto **7a**). Dentro de los sustituyentes aromáticos, las sustituciones *orto* se ven desfavorecidas frente a las *para* y se produce una mejora de la actividad con sustituyentes electroatractores (**7ma** Vs **7kf**). Además, la disposición relativa *trans* entre

los sustituyentes en C1 de las THiQ mejoran la actividad con respecto a los que presentan la disposición *cis* (compuesto **7ma** Vs **7ka**).

Comparando los compuestos con la función urea y los que poseen la piperazinadiona en su estructura, se concluye que estos últimos no poseen un efecto directo sobre el canal TRPM8 aunque sí producen un incremento de los niveles de Ca^{2+} intracelular, por lo que podrían producir la apoptosis en células tumorales.

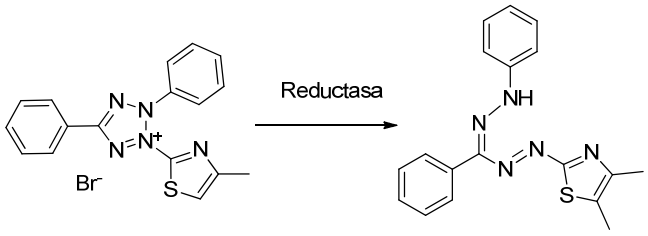
3.4.7. Mecanismo de acción: Apoptosis.

Los tres compuestos obtenidos con mejor valor de IC_{50} por su efecto antagonista son ensayados en la línea celular hormono-dependiente de cáncer de próstata, LNCaP.

Compuesto	Potency EC_{50} TRPM8 µM	IC_{50} inhibition TRPM8 µM (icilin 0.25 µM)	MTT Test at 5 µM (% control)	DNA test at 5 µM (% control)	MTT 3 exp average±SE
7kf	NA	0.51 ± 0.11	89.95 ± 3.10	74.87 ± 11.4	88.4 ± 2.5
21n	NA	0.65 ± 0.06	66.90 ± 4.36	66.28 ± 8.01	55.7 ± 5.7
7ka	NA	0.11 ± 0.01	85.78 ± 5.03	85.44 ± 8.22	84.9 ± 3.3

Tabla 3. 20

El test de MTT (bromuro de 3-(4,5-dimetiltiazol-2-il)-2,5-difeniltetrazolio, color amarillo) se basa en la reducción de este colorante en presencia de una enzima oxidoreductasa NAD(P)H-dependiente, que se encuentra en el citosol, para generar el compuesto químico llamado formazán (color purpura). Las medidas de absorbancia nos permiten cuantificar la actividad celular y estudiar la citotoxicidad de los compuestos. La reducción del MTT a formazan se incrementa con la actividad celular debido al incremento del NAD(P)H por lo que un efecto antagonista, que induce la apoptosis, debería generar una disminución de la actividad celular y por tanto del compuesto de referencia formazan (esquema 3.77).



Esquema 3. 77

Atendiendo a los datos del efecto antagonista sobre TRPM8, podemos observar que el compuesto con mayor citotoxicidad en los tres ensayos corresponde a **21n**, siendo los tres valores aceptables para proseguir el estudio SAR.

3.4.8. Conclusiones.

-La proteína TRPM8 se presenta como un novedoso canal intercambiador de cationes Ca^{2+} indispensable en los procesos de crecimiento celular. La implicación de este canal en la supervivencia celular así como la sobreexpresión del mismo en células tumorales le convierten en una diana terapéutica muy atractiva en la lucha contra el cáncer.

-Del estudio SAR realizado sobre estructuras que contienen la función urea, en un intento de emular agonistas y antagonistas de este canal, se desprenden las siguientes conclusiones:

a. La función urea (**3**) al igual que las THIQ (**7oa**) por si solas, no presentan actividad sobre estos canales.

b. La fusión de la función urea en el grupo amina que forma parte de una THIQ, arroja cierta actividad antagonista (**7d**).

c. La formación de THIQ en las dos funciones amina de una urea, con disposición relativa *trans* entre las posiciones C1 de ambas THIQ nos proporciona valores de IC_{50} del orden de 10^{-7}M, mientras que las disposiciones *cis* generan valores de 10^{-5}M. Estos resultados en los compuestos con disposición *trans* resultan muy prometedores.

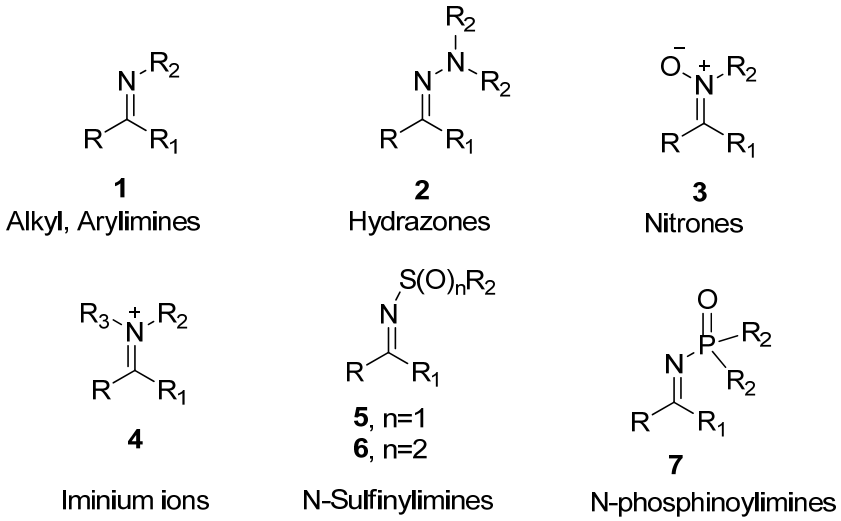
d. Estructuras de tetrahidropirazinoisoquinolinas han resultado potentes antagonista de estos canales siendo de destacar la importancia de la sustitución de los grupos metoxi en R_1 y R_4, en los anillos aromáticos A y E.

4. Chapter IV. English Summary.

4.1. Introduction.

4.1.1. Synthesis of and *N*-acyliminium ion derivatives.

Nucleophilic adition to carbon-nitrogen double bond is one of the most widely used methods for the synthesis of nitrogen derivatives[147]. In terms of reactivity, comparison with carbonyl group shows a lower electrophilicity of azamethine carbon.To overcome this limitation, several electrophilic systems have been developed though a proper choice of the nitrogen-linked group:



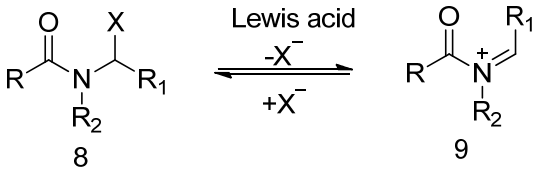
Scheme 1. 21

1. Alkyl or arylimines (**1**) and hydrazones (**2**) are sufficiently stable to be prepared and stored but these derivatives are not reactive enough and removal of the nitrogen-linked group after the addition is often a problem.
2. Nitrones (**3**) are more reactive than simple imine and their reaction with nucleophilic reagents affords secondary hydroxylamines[148].
3. An increase in reactivity can be achieved by preparation of iminium ions (**4**) by *N*-alkylation of imines[149].

[147](a) Volkmann, R. A. in *Comprehensive Organic Synthesis*; Schreiber, S.L., ed.; Pergamon: Oxford, **1991**; Vol. 1, p 355. (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (c) Bloch, *R. Chem. Rev*. **1998**, *98*, 1407. (d) Kobayashi, S.; Ishitani, H. *Chem. Rev*. **1999**, *99*, 1069

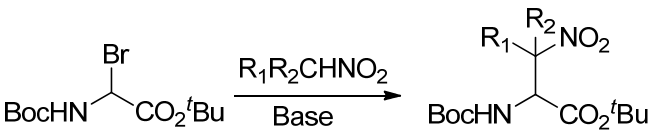
[148](a) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett*, **2000**, 442. (b) Lombardo, M.; Trombini, C. *Synthesis*, **2000**, 759.

4. *N*-sufinylamines (5 and 6, R^2=^{t}Bu, *p*-tolyl) combine the activating properties of the sulfynil group with the property of high diasterofacial selectivity nucleophilic additions[150].
5. *N*-phosphinoylimines have gained particularly importance in some catalytic processes leading to the preparation of enantioenriched primary amines[151].
6. Finally, *N*-acyliminium ions[152] are very electrophilic substrates although they are also very unstable to be prepared and stored and therefore they must be prepared *in situ.*
N-acyliminium ions can be reached from α-substituted amides that can be eliminated under suitable conditions[153]. This cation (**9**) can be stabilized when the acyl moiety is a carbamate (**8,** R=OR_3) probably due to the increased avalability of the carbamate nitrogen lone pair



Scheme 1. 22

α-Haloamides (X=Cl, Br) have found only occasional use due to their unstability[154].

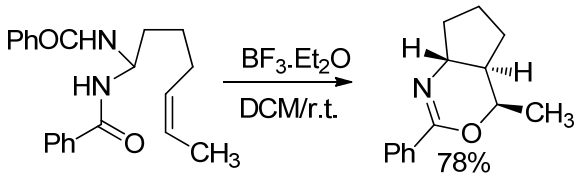


a.R_1=R_2=CH_3
b.R_1=R_2=H
c.R_1=$CH_2CO_2CH_3$, R_2=H

Scheme 1. 23

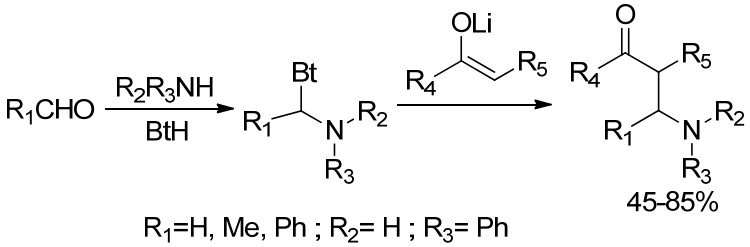
[149] (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem.* Int. Ed. Engl. **1998**, *37*, 1044. (b) Bur, S. K.; Martin, S. F. *Tetrahedron*, **2001**, *57*, 3221.
[150] (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Res.* **2002**, *35*, 984. (b) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003.
[151] (a) Spino, C. *Angew. Chem. Int. Ed*. **2004**, *43*, 1764. (b) Kohmura, Y.; Mase, T. *J. Org. Chem*. **2004**, *69*, 6329.
[152] (a) Maryanoff, B. E.; Zhang, H. C.;Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem.Rev*. **2004**, *104*, 1431. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron*, **2000**, *56*, 3817. (c) Hiemstra, H.; Speckamp, W. N. Comprehensive Organic Synthesis; Heathcock, C. H., Ed.; Pergamon: Oxford, 1991; Vol. 2, p 1047.
[153] Zaugg, H. A. *Synthesis* **1984**, *85*, 181.
[154] Coghlan, P. A.; Easton, C. J. *Tetrahedron Lett*. **1999**, *40*, 4745.

α-Oxygenated amides and carbamates (X=OR_3,$OCOR_3$) are the most exploited precursors of *N*-acyliminium ions. These derivatives are quite stable compounds and can be prepared by partial reduction of imides and other reactions on imines[155].
Bisamides (X=NHCOR) have been mainly used in cycloaddition reaction[156].



Scheme 1. 24

α-Amidoalkyl benzotriazoles[157] (X=benzotriazolyl) are readily prepared and are effective precursors of reactive intermediate **9**.



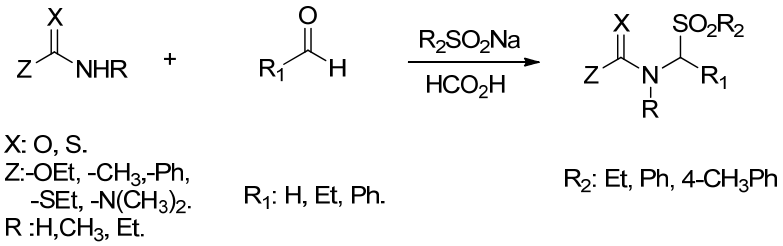
Scheme 1. 25

α-Amidosulfones (X=SO_2R), which have a good stability, are nevertheless suitable precursors to *N*-acyliminium ion because of the good leaving character of the RSO_2 group, especially in the presence of Lewis acids.[158]

4.1.2. α–Amide sulfones as a precursor of *N*-acyliminium ions.

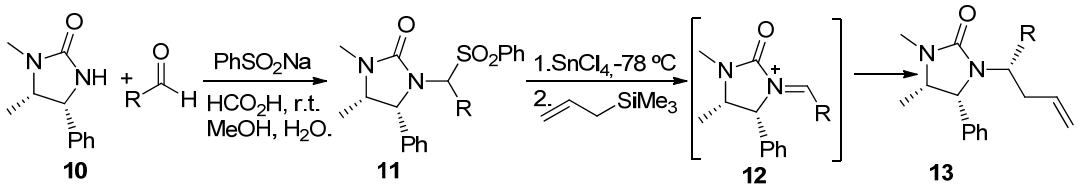
The three component coupling leading to the synthesis α-amido sulfones was pioneered in 1964 by Engberts and Starting who obtained a number of these sulfones by mixing ethyl carbamate, formaldehyde and sodium sulfinate in acidic conditions[159].

[155] De Koning, H.; Speckamp, W. N. Stereoselective Synthesis (Houben-Weyl); Helmchen, G., Hoffman, R. W., Mulzer, J., Shaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, **1995**, Vol. 2, p 1047.
[156] Weinreb, S. M.; Scola, P. M.; *Chem . Rev*. **1989**, *89*, 1525.
[157] Katritzky, A. R.; Manju, K.; Singh, S. K.;Meher, N. K.*Tetrahedron* **2005**, *61*, 2555.
[158] Nájera, C.; Yus, M.Tetrahedron **1999**, *55*, 10547.



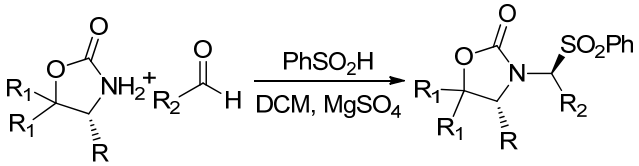
Scheme 1. 26

Later on, Pearson *et al.* [160] prepared chiral exocyclic α-amido sulfones from imidazolindin-2-one (**10**), using Engberts' conditions. The conversion of α-amidesulfones (**11**) into *N*-acyliminium ions proceeds in the presence of Lewis acids ($SnCl_4$) that assist the elimination of phenylsulfonyl group. Intermediate **12** then reacts with allyltrimethylsilane to afford the corresponding addition product **12**.



Scheme 1. 27

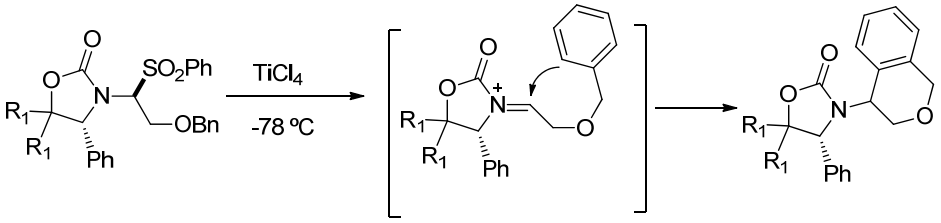
These classical conditions failed when starting from chiral oxazolidin-2-ones[161] Petrini's group made a modification in the reaction conditions ($PhSO_2H$, CH_2Cl_2, $MgSO_4$), that allowed the efficient preparation of the sulfone as a mixture of diastereomers.



Scheme 1. 28

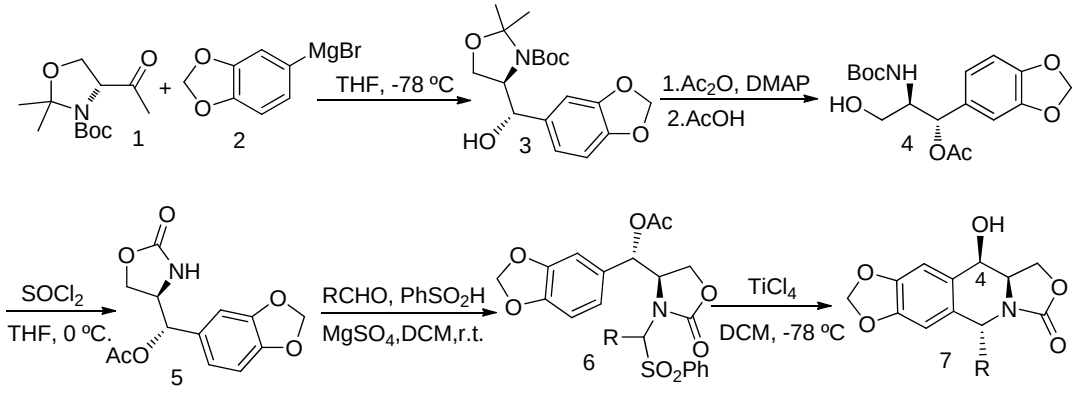
[159] Martin, S.F. *Acc. Chem. Res*. **2002**, *35*, 895.
[160] Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622.
[161] Marcantoni, E.; Mecozzi, T.; Petrini, M. *J. Org. Chem*. **2002**, *67*, 2989.

This chiral sulfone obtained from optically active 4-benzyloxazolidin-2-one can undergo an intramolecular ring closure[162]. following formation of the corresponding *N*-acyliminium ions.



Scheme 1. 29

This approach was used for the synthesis of aza-analogues of the anticancer drug podopoyllotoxin[163]. The reaction of Garner's aldehyde (**1**) with Grignard reagent (**2**) gave the alcohol **3,** with *anti* diastereoselectivity. Acetylation of the hydroxyl group followed by hydrolysis of the oxazolidine ring provides alcohol **4**, which is then converted into oxazolidin-2-one **5**. α-Amidosulfone **6** obtained from compound **4** upon treatment with $TiCl_4$ gave tricyclic derivatives **7** as single diastereomers. In these conditions, cleavage of the acetoxy group with silmultaneous epimerization at C-4 was also observed.



Scheme 1. 30

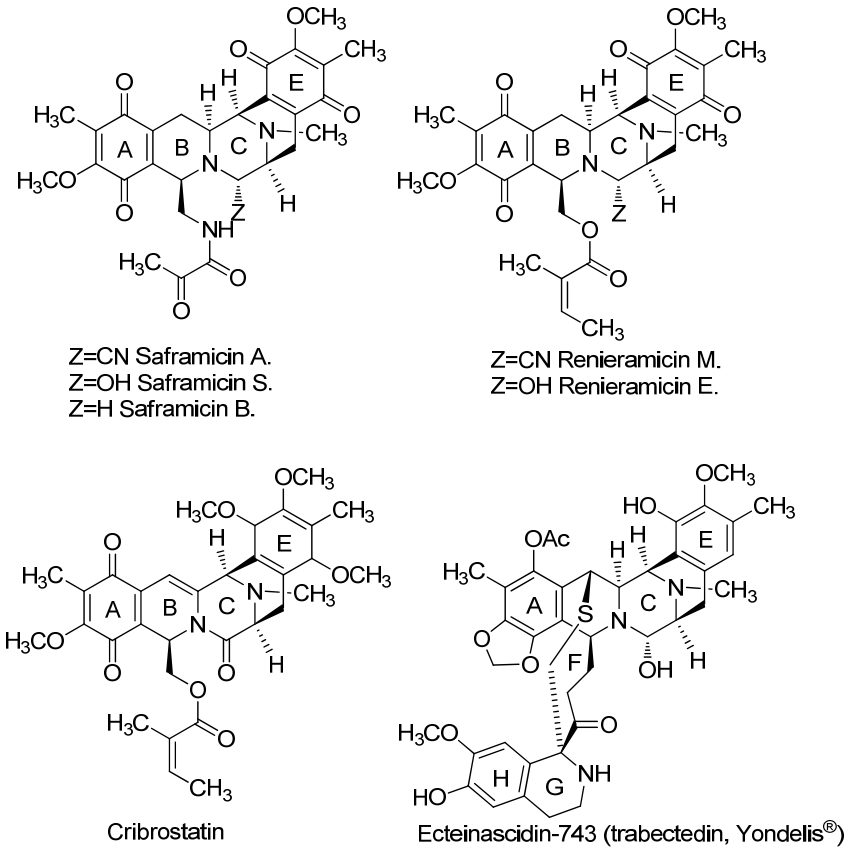
[162] Mecozzi, T.; Petrini, M.; Profeta, R. *Tetrahedron*: *Asymmetry*, **2003**, *14*, 1171.
[163] Marcantoni, E.; Petrini, M.; Profeta, R. *Tetrahedron Lett.* **2004**, *45*, 2133.

The structures obtained with this methodology have a tetrahydroisoquinoline core. This THIQ skeleton is present in many natural products including saframycins, renieramycins and the ecteinascidins. All these compounds have generated wide chemical and biological interest because of their novel structure and limited availability in nature and also due to their potent antitumor activity.

4.1.3. Tetrahydroisoquinoline alkaloids and their antitumor activity.

Alkaloids belonging to the tetrahydroisoquinoline family include a number of natural compounds that display a range of biological properties such as antitumor and antimicrobial activitiesSome of these compounds behave as potent cytotoxic agents, including the saframycins isolated from *Streptomyces lavendulae*[164], jorumicine isolated from *Jorunna funebris*[165], the reineramicins isolated from sponge *Reniera sp.* and *Xestospongia sp.* [166] the cribostatin isolated from *Cribochalina sp*.[167] and the ecteinascidin isolated from tunicate *Ecteinascidia turbinata*[168].

[164] Arai, T.; Takahashi, K.; Kubo, A. *J. Antibiot.* **1977**, *30*, 1015.
[165] Fontana, A.; Cavaliere, P.; Wahidulla, S.; Chandrakant, G. N.; Cimino, G. *Tetrahedron* **2000**, *56*, 7305.
[166] Suwanborirux, K.; Amnuoypol, S.; Plubrukarn, A.; Pummangura, S.; Kubo, A.; Tanaka, C.; Saito, N. *J. Nat. Prod.* **2003**, *66*, 1441.
[167] Pettit, G. R.; Collins, J. C.; Herald, D. L.; Doubek, D. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, D. L.; Tackett, L. P. *Can J. Chem.* **1992**, *70*, 1170.
[168] a) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Stroh, J. G.; Kieffer, P. A.; Sun, F.; Li, L. H.; Martin, D. G. *J. Org. Chem.* **1990**, *55*, 4512. b) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Stroh, J. G.; Kieffer, P. A.; Sun, F.; Li, L. H.; Martin, D. G. *J. Org. Chem.* **1991**, *56*, 1676.

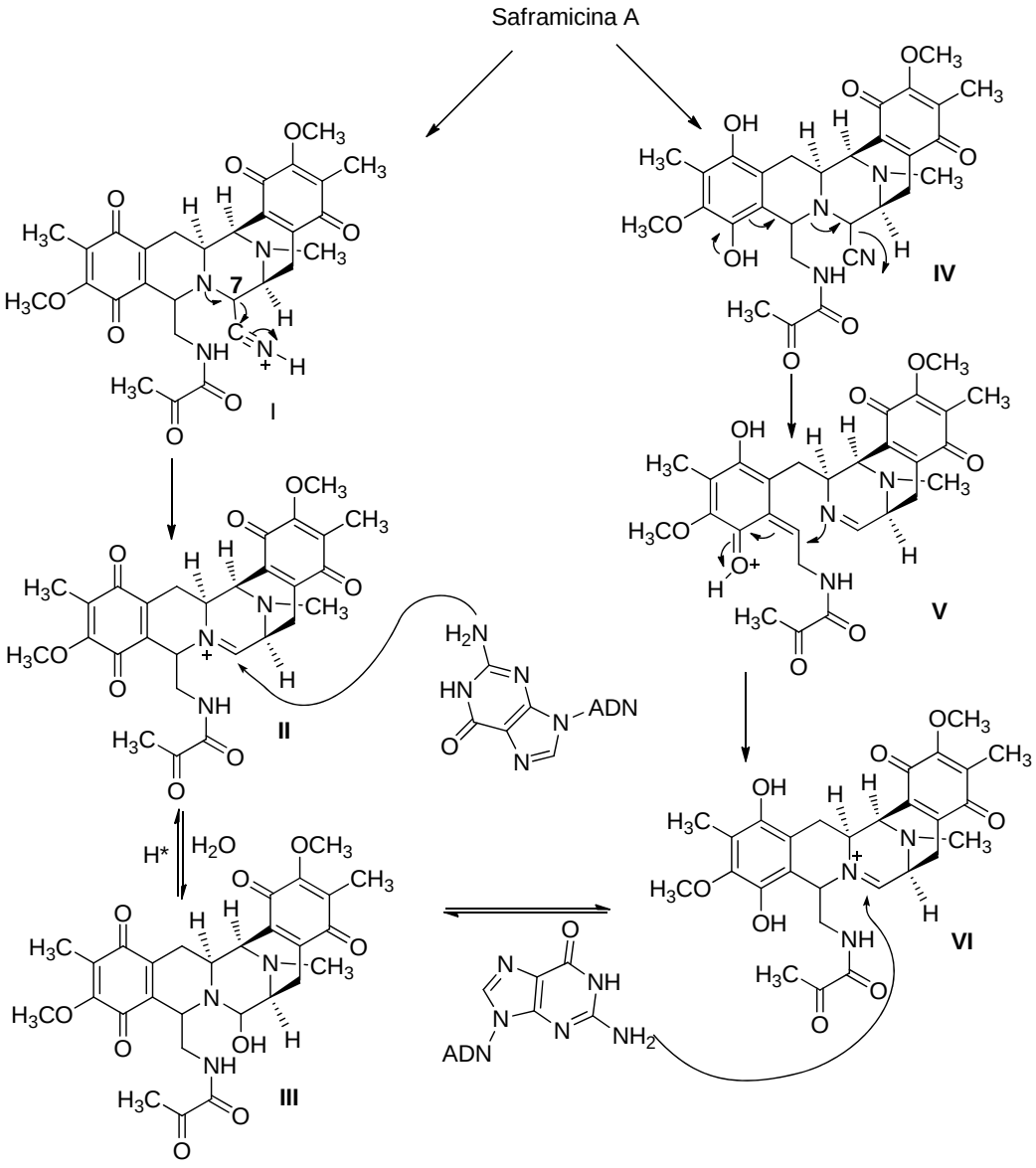


Scheme 1. 31

The ecteinascidins and saframicis families share a the core pentacyclic motifs that leads to the same mode of antitumor activity, based on DNA alkylation in the minor groove[169].
As several studies have shown, it is the presence of either a nitrile or a hydroxy group at C-7 (**I**) in closed proximity to a nitrogen atom that is critical for the biological activity of these natural products[170]. If these particular functional groups are activated through an event such as protonation, as shown in scheme 1.12 using saframycin A as a representative model, the neighboring nitrogen atom is suitably disposed to expel the leaving group affording the iminium cation (**II**). This reactive species could then be reversibly trapped by water[171] (**III**) or attacked by the free amine of a guanine residue in DNA. On the other hand, if the saframicin is reduced to its hydroquinone form (**IV**) before being engaged by

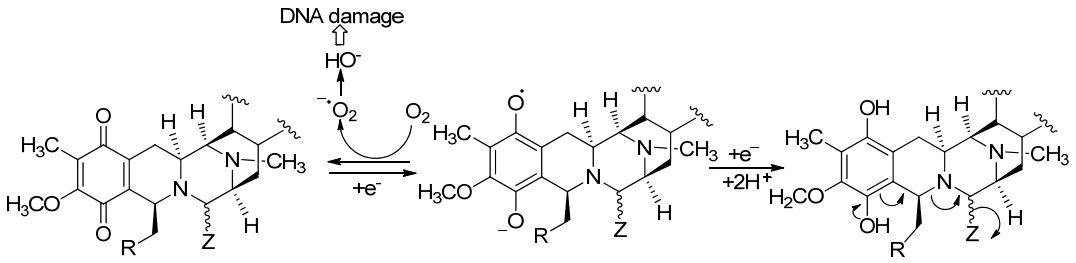
[169] Zewail-Foote, M.; Hurley, L. H. *J. Am. Chem. Soc.* **2001**, *123*, 6485.
[170] (a).Lown, J. W.;Joshua, A. V.; Lee, J. S.*Biochemistry* **1982**, *21*, 419.(b) Hill, G. C.; Remers, *J. Med. Chem.* **1991**, *34*,1990.
[171] Moore, R. M.; Seaman, F. C.; Wheelhouse, R. T.; Hurley, L. H. *J. Am. Chem. Soc.* **1998**, *120*, 2490.

the genetic material, the free phenol could lead to the cleavage of the nitrogen-bearing ring in combination with cyanide expulsion to afford a highly reactive *o*-quinone methide (**V**). A guanine residue in DNA could then either attacks this entity directly or its alternative iminium form (**VI**), thereby leading to the formation of a new covalent bond at C-7. Regardless of which mechanistic scenario prevails, this alkylation event in itself is insufficient to induce apoptosis since the formation of an diamino aminal is subject to thermal reversion.



Scheme 1. 32

Alternatively, saframycin in its hydroquinone form[172] can reduce molecular oxygen to superoxide which immediately leads to cellular death by DNA fragmentation (Scheme 1.13).



Scheme 1. 33

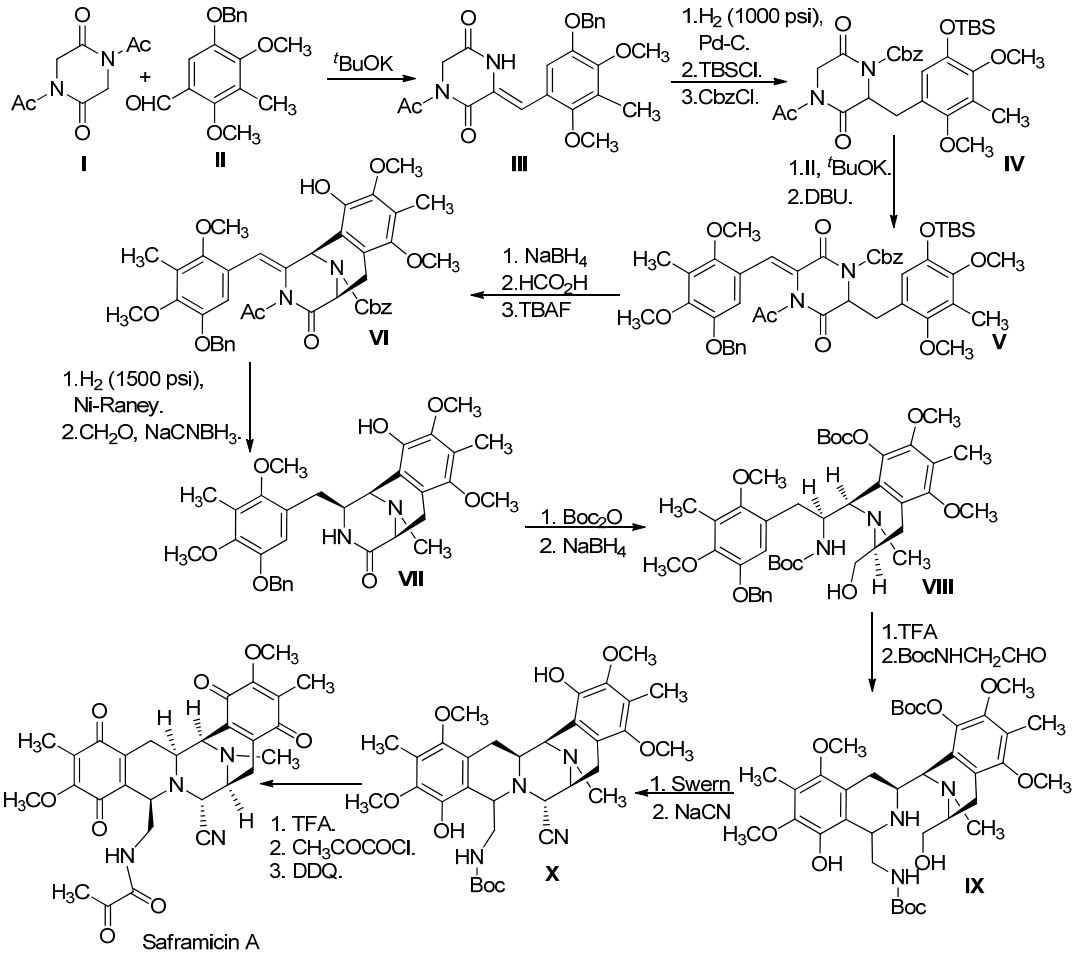
4.1.4. Synthesis of saframycins. ACED-B strategy.

The first synthesis of saframycin B was reported in 1990 (Scheme 1.14) by Fukuyama *et al.*[173] starting with aromatic aldehyde **II**, which was treated with the potassium enolate of diketopiperazine **I** to form **III** in 86% yield. These reaction conditions removed one of the acetyl groups, allowing the selective protection of the amide thus uncovered as a Cbz carbamate to afford compound **IV**. Following a second aldol condensation with aldehyde **II**, the *N*-Cbz-protected diketopiperazine was selectively reduced to the carbinolamine using sodium borohydride. This allowed the cyclization via iminium ion upon treatment with formic acid to afford tricycle **VI.** High-pressure hydrogenation over Raney-Ni followed by amine methylation yielded **VII** in 85% yield. The lactam was activated via protection of the lactam nitrogen as the corresponding *tert*-butyl carbamate. The lactam carbonyl was then reduced under mild conditions to afford **VIII.** Removal of the *tert*-butyl carbamate was followed by a Pictet-Spengler reaction, affording the pentacyclic core. Swern oxidation of the primary alcohol afforded the corresponding aldehyde, which was trapped intramolecularly by the secondary amine to form an intermediate carbinolamine that was trapped with sodium cyanide to form the stable amino nitrile **IX**. The final step of

[172] (a) Ishiguro, K.; Sakiyana, S.; Takahashi, K.; Arai, T. *Biochemistry* **1978**, *17*, 2545. (b) Ishiguro, K.; Takahashi, K.; Yazawa, K.; Sakiyana, S.; Arai, T. *J. Biol. Chem*. **1981**, *256*, 2162. (c) Hill, G. C.; Remers, W. A. *J. Med. Chem*. **1991**, *34*, 1990.

[173] Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am. Chem. Soc*. **1990**, *112*, 3710.

the synthesis involved cleavage of the *tert*-butyl carbamate, amide formation using pyruvyl chloride, and oxidation of the hydroquinones to quinones using DDQ, thus affording (±) -saframycin A.



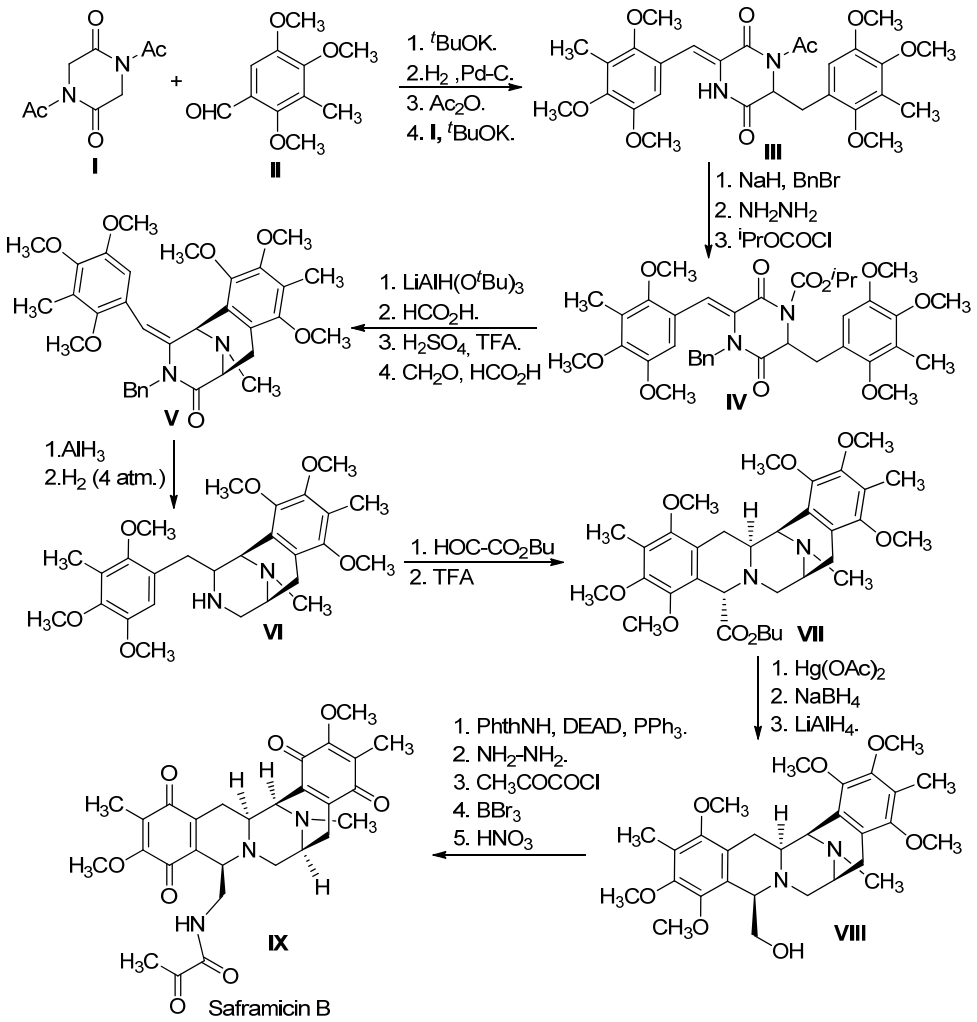
Scheme 1. 34

In 1987, Kubo *et al.* reported their synthesis of (±) -saframycin B[174] (Scheme 1.15). Aromatic aldehyde **II** was condensed with diketopiperazine **I**, followed by hydrogenation

[174] a) Kubo, A.; Saito, N.; Yamauchi, R.; Sakai, S. *Chem. Pharm. Bull.* **1987**, *35*, 2158. b) Kubo, A.; Saito, N.; Yamato, H.; Kawanami, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2525. c) Kubo, A.; Saito, N.; Nakamura, M.; Ogata, K.; Sakai, S. *Heterocycles* **1987**, *26*, 1765. d) Kubo, A.; Saito, N.; Yamato, H.; Yamauchi, R.; Hiruma, K.; Inoue, S.

of the exocyclic olefin. A second aldol condensation provided **III** in 52% overall yield for the three steps. Selectivea activation of one of the lactam carbonyls was accomplished via the benzyl protection of the unprotected lactam followed by acetate removal and carbamate formation to afford **IV**. Partial reduction of the activated lactam **IV** was accomplished using lithium aluminum tri-*tert*-butoxyhydride. Cyclization of the carbinolamine was achieved using formic acid as in Fukuyama's synthesis. Removal of the isopropyl carbamate followed by *N*-methylation yielded tricycle **V** in 50% yield. Tricycle **V** was converted to pentacycle **VI** via reduction of the amide to the amine using alane followed by hydrogenation of the exocyclic olefin and hydrogenolysis of the N-benzyl substituent followed by a Pictet-Spengler cyclization. Unfortunately, the stereochemistry obtained at the B-ring stereocenter was the undesired one. Epimerization of this center was accomplished by oxidation of the amine to the imine using Mercury(II) acetate followed by selective reduction of the imine from the least hindered face using $NaBH_4$. The butyl ester was reduced using LAH to afford **VII** in 55% yield over the three steps. Amination of the alcohol was accomplished via a Mitsunobu reaction using phthalimide. The phthalimide protecting group was removed, and the amine was acylated with pyruvyl chloride to yield **VIII**. The final two steps were demethylation of the hydroquinones using boron tribromide followed by oxidation to the quinone stage using 10 M HNO_3 to provide saframycin B in 41% yield for the last two steps.

Chem. Pharm, Bull. **1988**, *36*, 2607. e) Kubo, A.; Saito, N.; Yamato, H.; Masubichi, K.; Nakamura, M.; *J. Org. Chem.* **1988**, *53*, 4295.



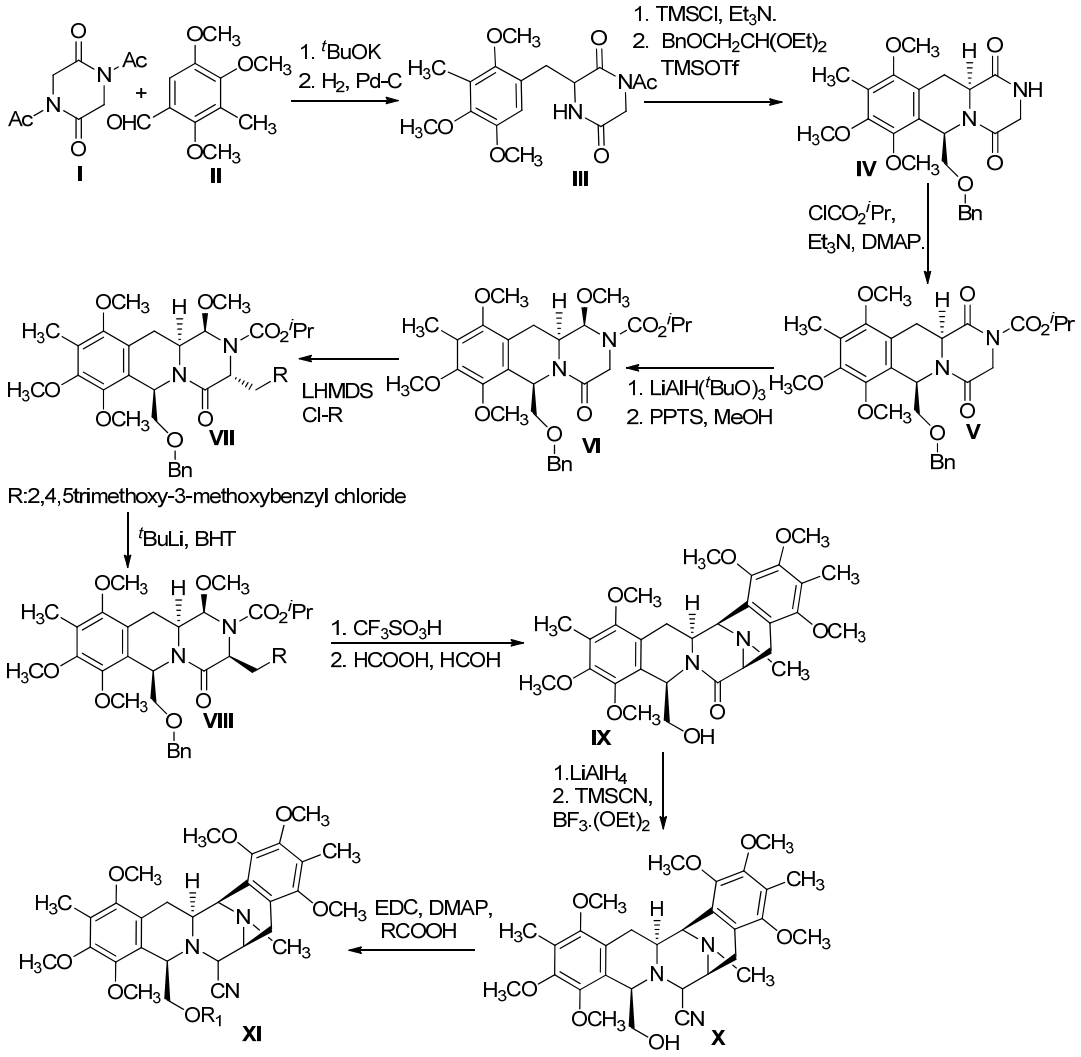
Scheme 1. 35

4.1.5. Synthesis of saframycins. ACEB-D strategy.

This methodology was followed by Avendaño's group[175] to reach saframycin analogues (Scheme 1.16). Aldol condensation between aldehyde **II** and diketopiperazine **I** and followed by hydrogenation of the unsaturation to give **III** in 97 % yield. Ring closure through a modified Pictet Spengler cyclization furnished the tricycle **IV** with the desired

[175] (a) Ortín, I.; González, J. F.; De la Cuesta, E.; Avendaño, C. *Bioorganic & Medicinal Chemistry* ,**2010**, *18*, 6813. (b) Ortín, I.; González, J. F.; De la Cuesta, E.; Avendaño, C. *Tetrahedron* **2009**, *65*, 2201. (c) Ortín, I.; González, J. F.; Manguan-García, C.; Rosario Perona, R.; De la Cuesta, E.; Avendaño, C *Bioorganic & Medicinal Chemistry* **2008**, *16*, 9065.

stereochemistry. The activation of the lactam group via carbamate formation afforded **V**. The selective reduction over C1 followed by introduction of a methoxy group in this position gave **VI**, and its alkylation at C3 using 2,4,5-trimethoxy-3-methoxybenzyl chloride led to **VII**. In this alkylation the undesired stereochemistry was obtained, and therefore, C3 epimerization using a hindered base was needed, affording **VIII.** The cyclization of D ring was reached using a super-acid to complete the pentacyclic skeleton, and then a reductive formylation reaction gave **IX** in 79%yield over the two steps. The partial reduction of the amide to the carbinolamine was followed by treatment with *trimethylsilyl* cyanide to form **X** (52%). Finally, the primary alcohol was converted into an ester **XI** (62%) using a carbodiimide as coupling agent.

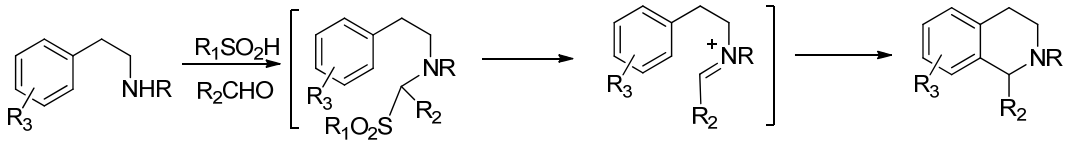


Scheme 1. 36

4.2. Aims

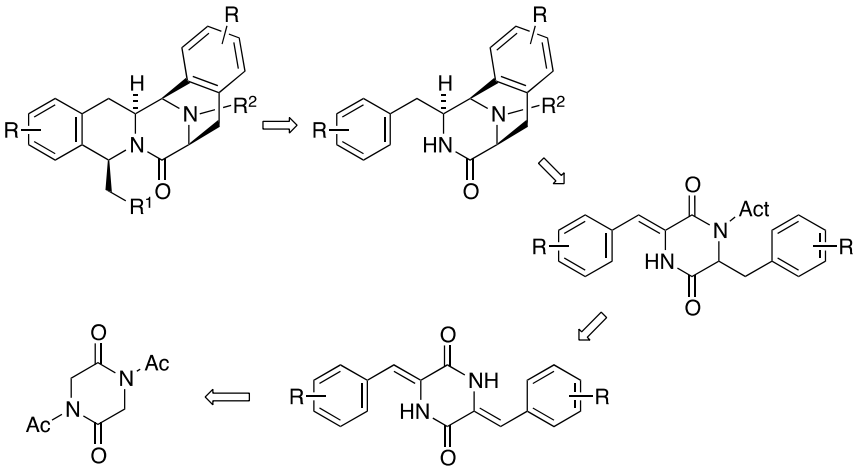
Despite the considerable number of known methodologies that allow access to the pentacyclic system of saframycins, it is still necessary to develop new approaches leading to simplified, shorter syntheses. A detailed study of the structures of the alkaloids reveals that most of them are made up of two identical tetrahydroisoquinoline units linked to a central piperazine. This hidden symmetry allows the design of simplified synthetic routes based on the use of symmetric starting materials, and the main aim of this Dissertation is the examination of two strategies aimed at achieving this goal. Against this backdrop, the main aims of the Thesis are summarized below.

1). The key step in several synthetic routes described to obtain saframycins involves the formation of the tetrahydroisoquinoline core. Our first aim was to discover, optimize and develop a method to obtain this heterocyclic scaffold using α-amidosulfones as intermediates, together with a study of the scope and limitations of this reaction. This method can be considered as a modification of the Pictet-Spengler reaction.



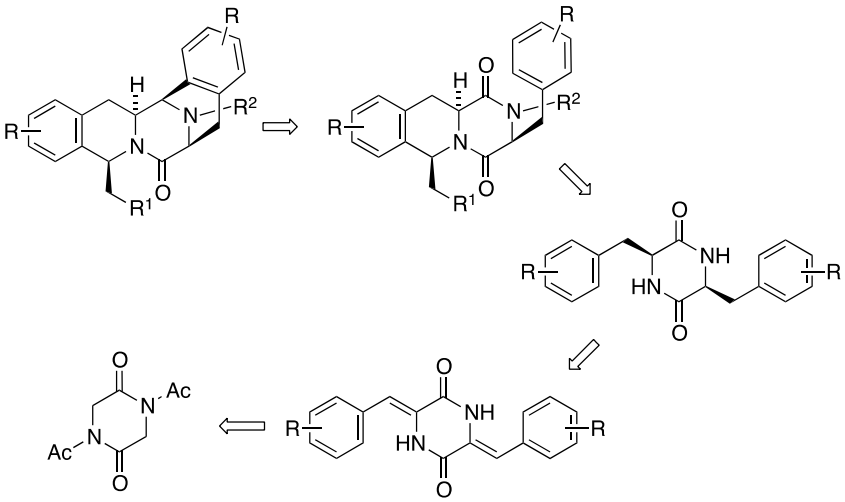
Scheme 2. 5

2). Our second aim was to break the symmetry inherent to 3,6-bis(arylmethylene)-2,5-piperazinedione by selective reduction of one of the exocyclic double bonds, allowing the construction of ring D. This would be followed by completion of the pentacyclic framework by closure of ring B through α-amidosulfone-type Pictet-Spengler reaction.



Scheme 2. 6

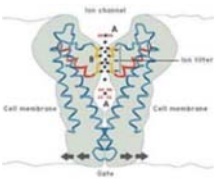
3). We also aimed at studying a second symmetry-based route, starting with the synthesis of ring B through our methodology based on the use of α-amidosulfone intermediates and the generation of ring D as the final step.



Scheme 2. 7

4) In order to achieve the aims described above, a number of problems need to be addressed, including the development of conditions leading to the desired configuration of the B-ring stereocenter. Also, it is necessary to develop a methodology allowing the functionalization of the saframycin C9 side chain.

5) A final objective was the discovery of new tetrahydroisoquinoline-derived hit compounds directed to the TRPM8 calcium channel, an emerging anticancer target, and the establishment of structure-activity relationship (SAR) of the analogues synthesized.



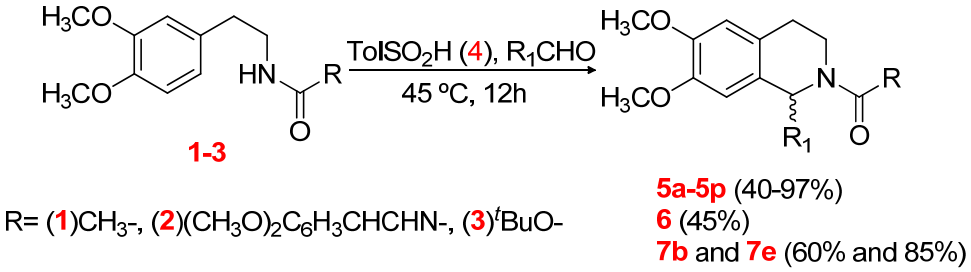
Scheme 2. 8

4.3. Results and Discussion.

4.3.1. A new synthesis of tetrahydroisoquinolines and its mechanistic study

4.3.1.1. A new methodology in THIQ synthesis *via* α-Amidosulfone intermediates.

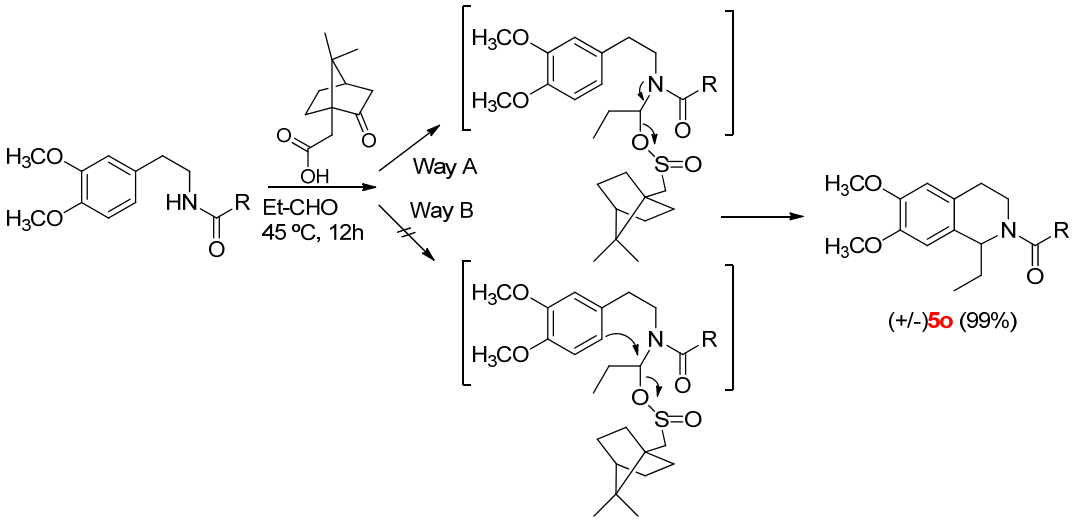
The first attempt to reach the tetrahidroisoquinoline core using α-amidosulfone intermediates was applied to several acyl derivarives of the commercially available homoveratrilamine.



Scheme 3. 1

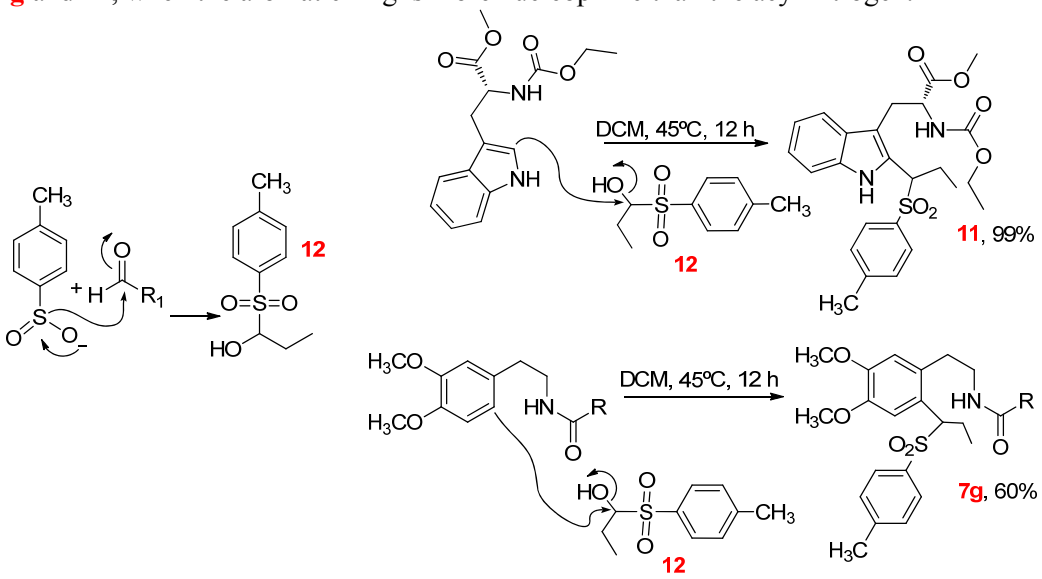
A high electron density in nitrogen leads to the highest yields in ring closure. The presence of electron-withdrawing or electron-releasing substituents in the aldehyde did not cause any difference in yield (**5c** and **5i**, 88%) but when these aryl aldehydes presented *ortho* sustitution in the aromatic ring, the steric hindrance led to lower yields (**5k**, 41% and **5m**, 57%).

In an attempt to ascertain whether the nucleophilic substitution proceeds via S_N1 or S_N2 mechanisms, we used a chiral catalyst (**9**). The fact that **5o** was obtained in racemic form shows that the pathway followed by this reaction involves a S_N2 mechanism (pathway B), since some enantioselection would have been expected from an S_N1 reaction (pathway A).

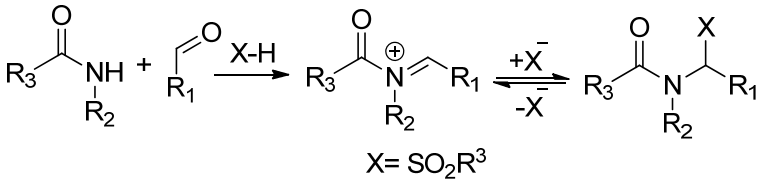


Scheme 3. 2

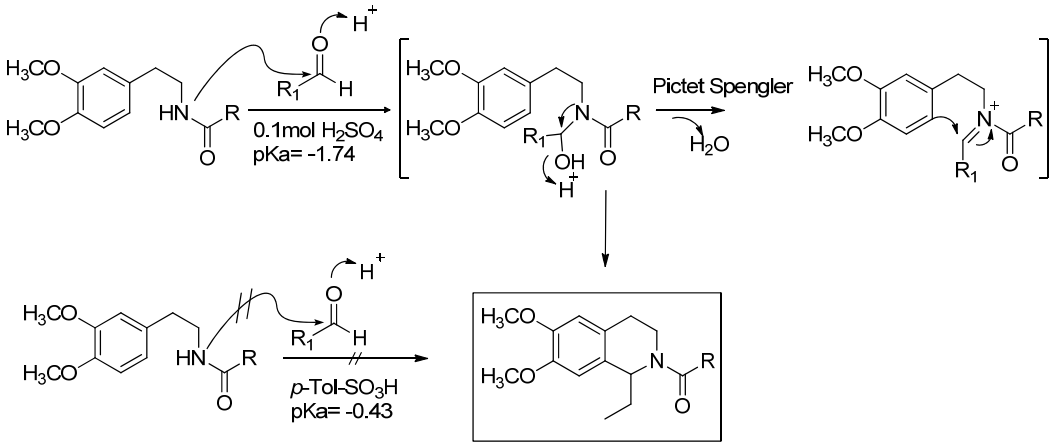
For the generation of the α-amidosulfone, we propose a mechanism going through the formation of intermediate **12.** This proposal is based upon by the isolation of compounds **7g** and **11**, when the aromatic ring is more nucleophilic than the acyl nitrogen.



This mechanism differs from the one proposed by Petrini's one[176], in which the iminium cation is attacked by the sulfinic acid to afford the α-amidosulfone.



Also we wanted to probe if the Brønsted acidity of the medium could be the reason of the cyclization. This possibility was discarded by the fact that *para*-toluenesulfonic acid (pKa= -0,43) could not close the ring whereas the use of the sulfinic acid (pKa = 1,48) afforded the cyclized product.

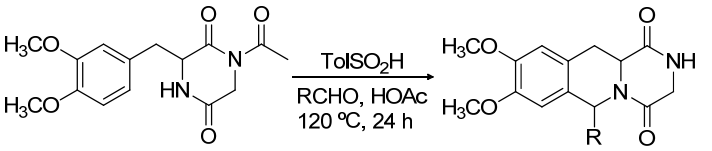


[176] Petrini, M. *Chemical Reviews*, **2005**, *105*, 11.

4.4. α-Amidosulfones in the saframicin synthesis. ACE-D-B strategy.

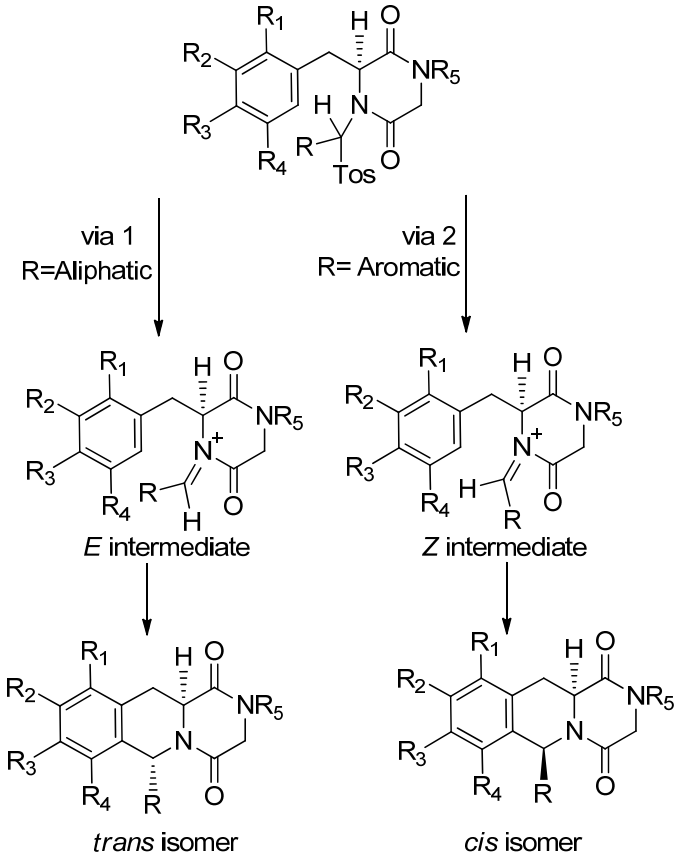
4.4.1. Model studies on a AC-B system.

B-ring formation was assayed on a 3-arylmethyl-2,5-piperazinedione derivative, which was transformed into compounds **16**. We found that the reaction affords the *trans* isomers when starting from aliphatic aldehydes, whereas aromatic aldehydes led to the *cis* isomer



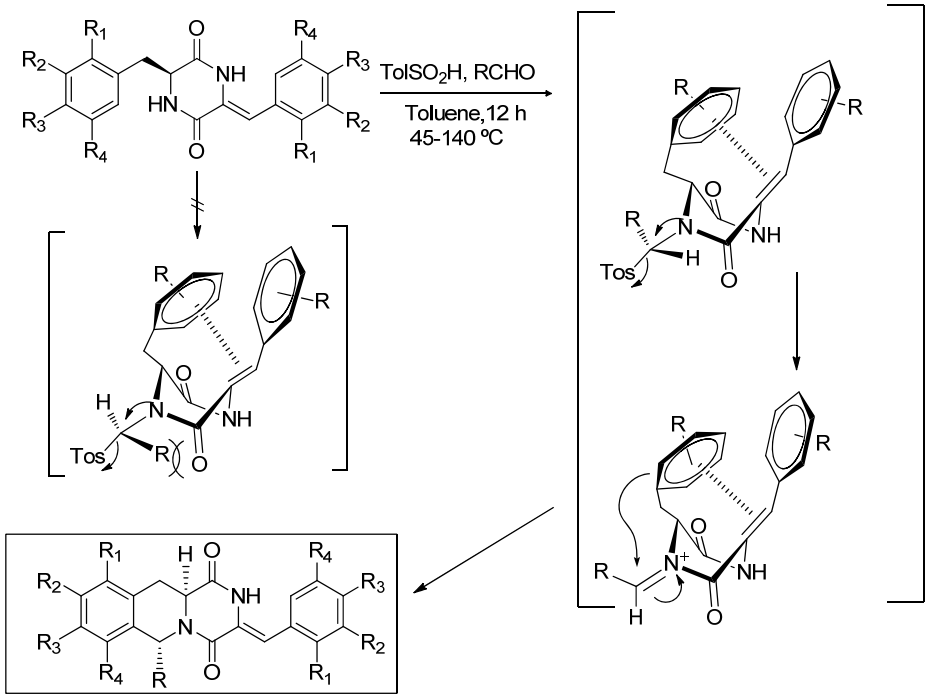
R=Et-, Ph-,*p*-BrC_6H_4-.
16a-16c

The isolation of *cis* products from the reactions involving aromatic aldehydes can be ascribed to π-stacking effects between the ring A and the aldehyde aromatic ring, which stabilize the *Z* iminium intermediate.



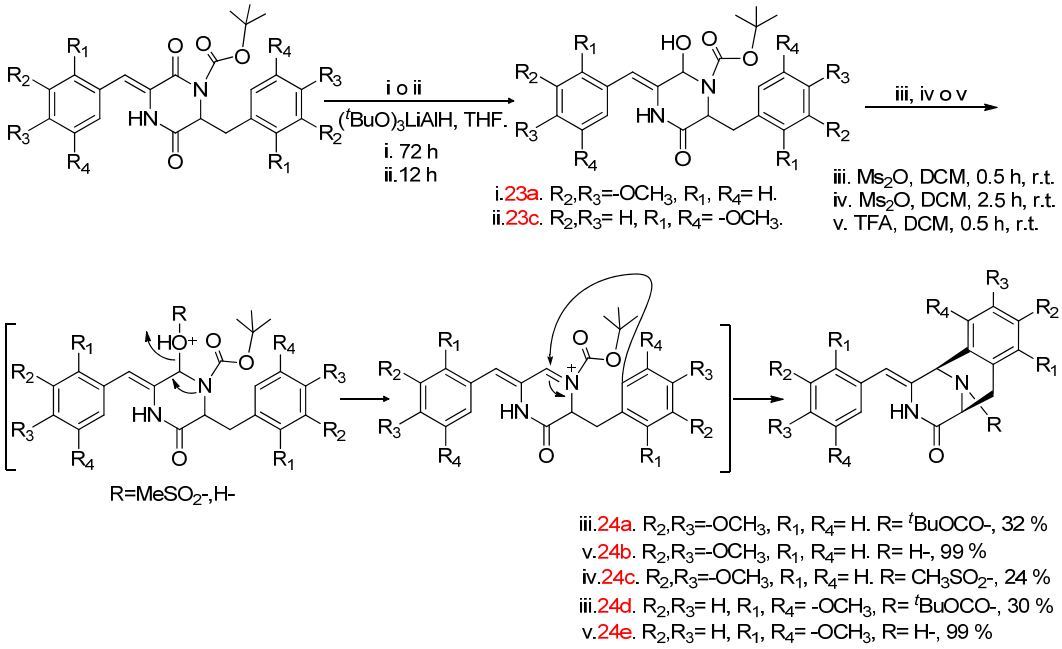
4.4.2. Preparation of ACE-B systems.

Ring closure to obtain ring B from unsaturated ACE systems through an α-amidosulfone intermediate led to compounds in the *trans* configuration. This can be explained through a π-stacking interaction of ring A with the unsaturated chain, allowing the formation of an *E* iminium intermediate.



4.4.3. Synthesis of ring D.

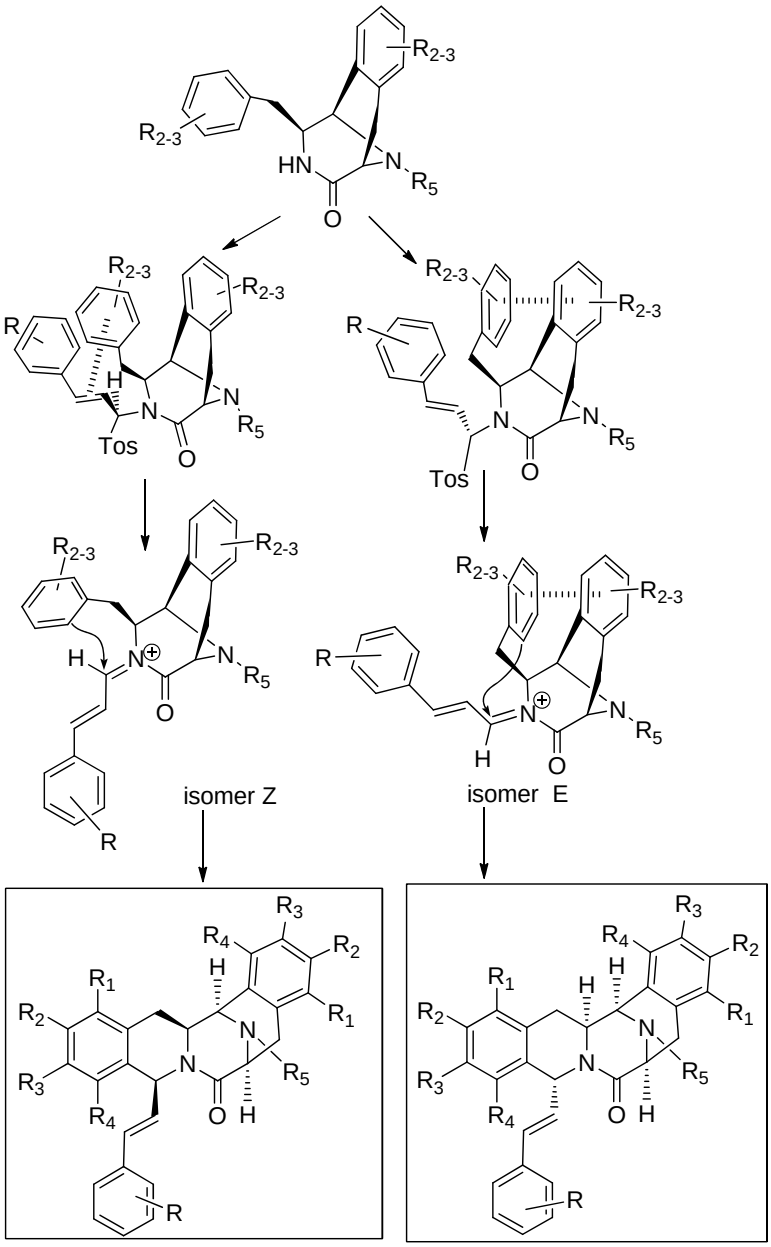
The increase in electrophilicity at C1 in the activated unsaturated ACE derivatives allows the nucleophilic attack of hydride to the carbonyl in this position and the formation of an unstable carbinolamine. This intermediate evolved to an iminium cation, which underwent an intramolecular Mannich-type reaction to generate ring D.



4.4.4. Synthesis of ring B.

To achieve cyclization of ring B, we found it necessary to use an aldehyde bearing an spacer between the reactive nitrogen and the aromatic ring to reduce the steric compression in the closure of ring B, and to this end we chose cinnamaldehyde as substrate. These reactions afforded mixtures of diastereoisomers, with the *cis* compound being normally major. Interestingly, the diastereoselection was found to depend on the reaction concentration, with some reactions giving predominantly the *trans* isomer when carried out in dilute solutions.

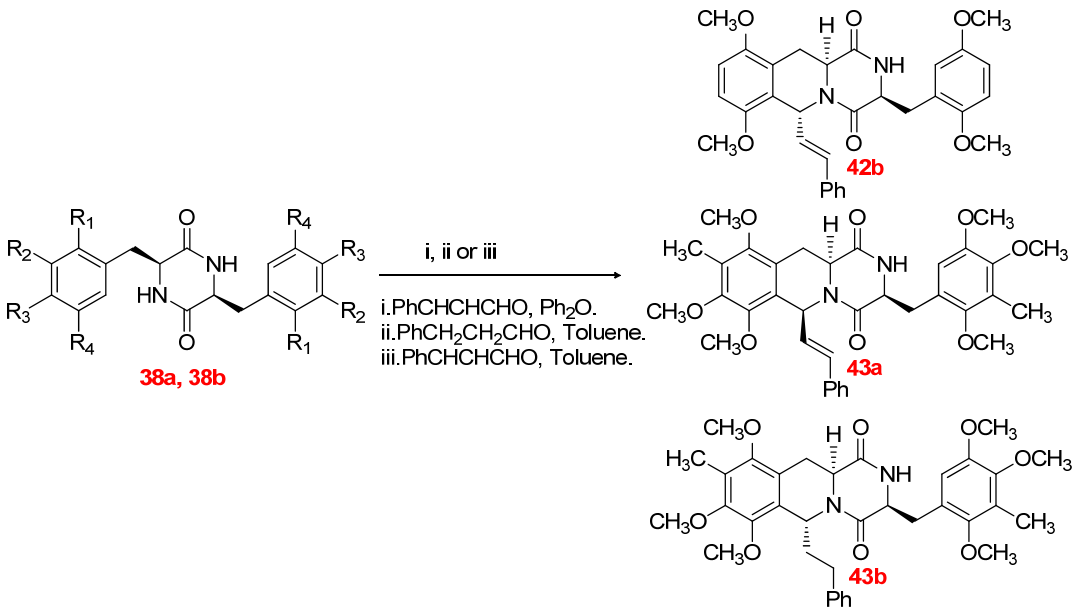
Our explanation for this stereochemical outcome is based on the interaction of ring A with ring E or with the unsaturation inside the cinnamaldehyde, with an influence from the ring A substituents.


R2-3
HN
N
R5
O
Tos
H
R
isomer Z
isomer E
R1
R2
R3
R4

4.5. α-Amidosulfones in saframycin synthesis. ACE-B-D strategy.

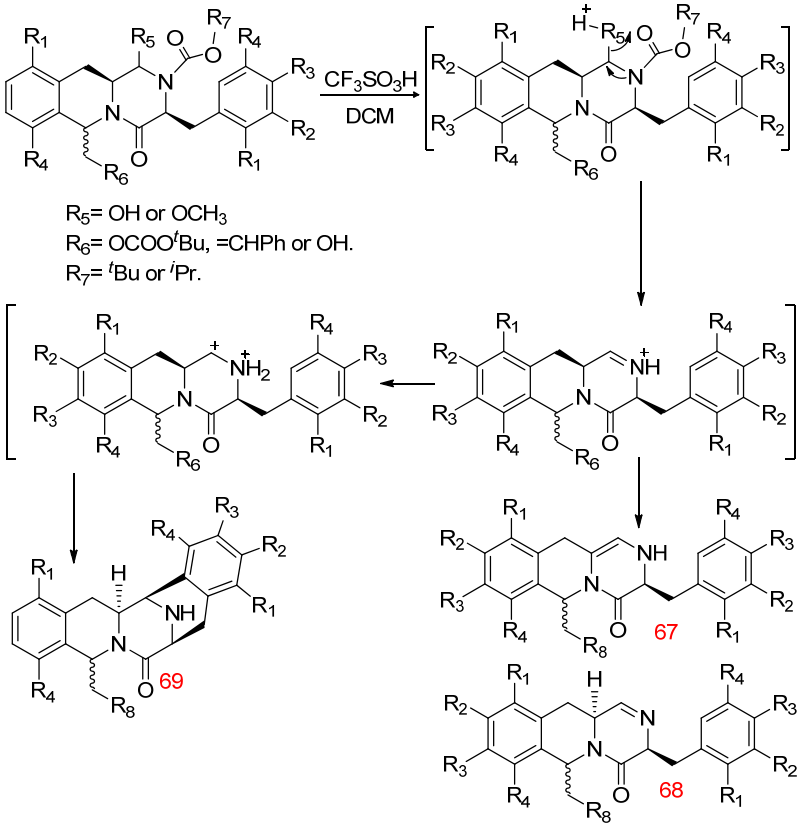
4.5.1. Synthesis of ring B.

It was possible to achieve the regio and diastereoselective α-amidosulfone-based Pictet-Spenglet-type cyclization of compounds **38a** and **38b** to yield the tricycles **42b**, **43a** or **43b**. The stereochemistry shown by these structures depends on whether the π-stacking is generated between ring A and ring E (leading to the *trans* compound **42b**) or between ring A and the styryl unsaturation (leading to the *cis* isomer **43a**). The different relative configuration of compounds **42b** and **43a** can be ascribed to a greater steric hindrance in the E ring of tne precursor to 43a, which hampers the ring A-ring E interaction and leads to the formation of an *E* iminium intermediate, which is the precursor to the *trans* diastereomer.



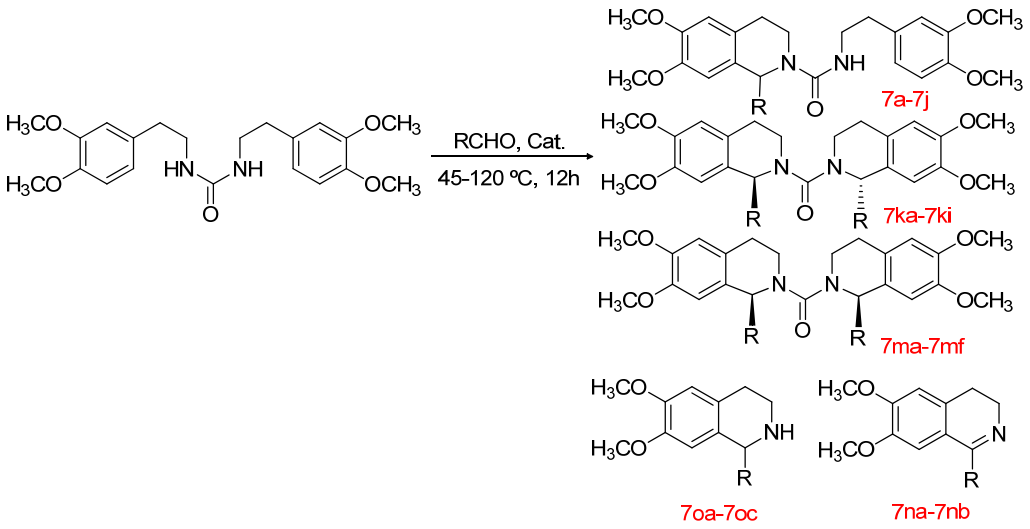
4.5.2. Synthesis of ring D.

For ring D closure, C1 must be first activated by generation of a carbamate group followed by its chemoselective partial reduction to an aminal and treatment with a superacid such as a triflic acid to generate the necessary double cation intermediate. If other conditions are used, the imino or enamino compounds **67** and **68** are obtained. It is also essential to have a styryl chain in C6 to reach the pentaciclic skeleton **69**.


CF3SO3H
DCM
R5= OH or OCH3
R6= OCOO^tBu, =CHPh or OH.
R7= ^tBu or ^iPr.
67
68
69

4.6. TRPM8, a new target to treat cancer.

TRPM8 is a cation channel belonging to the TRP (Transient Receptor Potential) family that can be activated by cold stimuli or by small-molecule ligands.
It has been reported evidence from immunofluorescence experiments that in the androgen-responsive LNCaP cell line, the TRPM8 protein is expressed in the endoplasmic reticulum and plasma membrane, and it acts as a Ca^{2+}-permeable channel. It has also been demonstrated that, TRPM8 channels are required for cell survival.
The moderate levels of TRPM8 found in normal tissue are increased in prostate cancer. Notably, trp-m8 mRNA was also expressed in a number of nonprostatic primary breast, colon, lung, and skin tumors but was hardly detected or not detected at all in the corresponding normal human tissues.
With the aim of gaining further insight into the functional and pharmacological properties of thermo-TRPM8 and in an attempt to identify compounds with the ability to be TRPM8 agonists and antagonists a series of urea-derived compounds ~~that~~ were synthesized and tested as TRPM-8 ligands (**7a-7j**). Some of these compounds showed moderate activity as antagonists and very low agonist activity.



A second series of BisTHI ureide compounds was then synthesized (**7ka-7ki** and **7ma-7mf**). These structures exhibited a significant antagonist activity, the most potent one being **7ka** with a *trans* relative configuration between H1 and H1''.

5. Capitulo V.Parte experimental.

Consideraciones generales.

Disolventes, reactivos y técnicas generales.

- *Disolventes y reactivos*

Todos los reactivos y disolventes comerciales se purificaron, cuando fue necesario, según los métodos descritos por Perrin y col.[177]

- *Técnicas generales*

Las reacciones sensibles al aire se realizaron bajo atmósfera de argón utilizando técnicas de Schlenk estándar. La purificación de los crudos de reacción se llevó a cabo por cromatografía en columna flash utilizando gel de sílice (0.2 mm de espesor) Merck 60 F_{254} y como eluyente el indicado en cada caso. El progreso de las reacciones se siguió por cromatografía en capa fina (cromatofolios de gel de sílice 60 230-400 mesh ASTM), utilizando para su revelado luz UV (l = 254 y 366 nm).

La temperatura de los experimentos se controló mediante el empleo de termómetros electrónicos IKA ETS-D4 y SENSOTERM P SELECTA, así como con el criostato HAAKE EK90.

Técnicas instrumentales.

Espectros de RMN: Los espectros de ^{1}H-RMN y ^{13}C-RMN se han realizado en aparatos Bruker AC 250 (250 MHz para ^{1}H y 63 MHz para ^{13}C), Bruker DPX 300 (300 MHz para ^{1}H y 75 MHz para ^{13}C), Bruker AMX 500 (500 MHz para ^{1}H y 125 MHz para ^{13}C) y Bruker AVIII 700 (700 MHz para ^{1}H y 175 MHz para ^{13}C). Los disolventes empleados fueron Cl_3CD y MeOD. Los desplazamientos químicos se expresan en ppm (d) y las

[177] Perrin, D. D.; Armarego, W. L. en "*Purification of Laboratory Chemicals*", 4ª ed. Pergamon Press: Oxford 1997.

constantes de acoplamiento en Hz. La multiplicidad de las señales se expresa como sigue: singlete (s), singlete ancho (bs), doblete (d), triplete (t), multiplete (m), doblete de dobletes (dd) y septuplete (sept). Los espectros de ^{13}C-RMN se realizaron con desacoplamiento total de protón, y se realizaron DEPT adicionales para la asignación de los diferentes tipos de carbono. Sólo se asignan las señales basadas en experimentos de correlación ^{1}H-^{13}C.

Los análisis elementales se realizaron por el Servicio de Análisis Elemental de la Universidad Complutense de Madrid.

Los espectros de masas se han registrado en el servicio de Espectroscopía de Masas de la UCM.

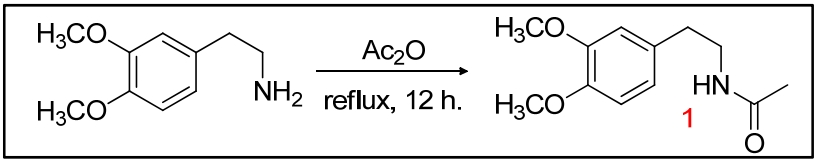
Los espectros de infrarrojo se realizaron en película en un espectrofotómetro Perkin-Elmer 1000 FT-IR. Los datos proporcionados corresponden a las absorciones más significativas y se expresan en cm^{-1}.

Los puntos de fusión fueron medidos en un aparato Reichert Autria y en un tubo capilar en un aparato Bibby-Stuart Scientific (meeting point apparatus SMP3) y están sin corregir.

Las hidrogenaciones a presiones superiores a una atmósfera se realizaron en un Parr Hydrogenation Apparatus, Mod: 5KC36LN19JT.

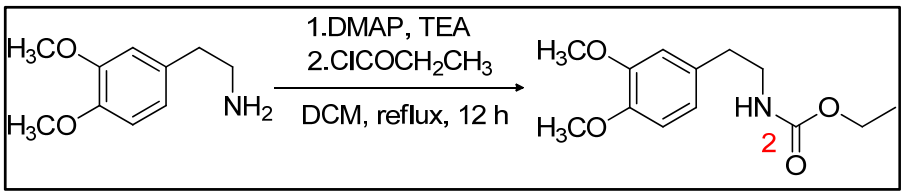
5.1. Synthesis 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives.

5.1.1. Synthesis and characterization of *N*-(3,4-dimethoxyphenethyl) acetamide 1.[178]



A solution of the commercial available homoveratrilamine (2.70 mL, 0.016 moles) in acetic anhydride (15 mL) was heated to reflux for 12 h. Then the mixture was concentrated *in vacuo* and the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with DCM (3 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give compound 1 as a brown oil, 94% yield.

5.1.2. Synthesis and characterization of *N*-(3,4-dimethoxyphenethyl) propionamide 2.

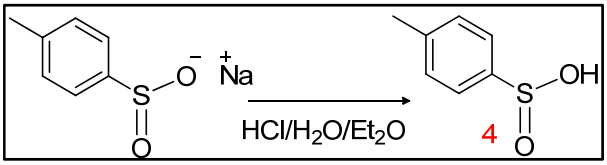


A solution of the commercial available homoveratrilamine (4.6 mL, 0.028 moles), and DMAP (0.34 g, 2.80 mmol) in dry DCM (10 mL), while was stirred, was added dropwise ethyl chloroformiate (5.0 mL, 0.038 mol) and Et_3N (3.90 mL, 0.028 moles) under Ar atmosphere at room temperature. Then the mixture was heated to reflux for 4 hours. The reaction was quenched with 1.0 N HCl and extracted with $CHCl_3$ (2x 50 mL). The organic

[178] Mor, M.; Rivara, S.; Silva, C.; Bordi, F.; Plazzi, P. V.; Spadoni, G.; Diamantini, G.; Balsamini, C.; Tarzia, G.; Fraschini, F.; Lucini, V.; Nonno, R.; Stankov, B. M.; J Med Chem. **1998** ;*41*, 3831

layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a brown oil. The crude was purified by flash column chromatography using a mixture 9:1 ethyl acetate:methanol to give compound **2** (6.44 g, 0.027 moles) as a brown oil, 96% yield. **IR (NaCl) ν_{max}** 2963, 2933, 2360 cm^{-1}; **Analysis**: Calcd. for $C_{13}H_{19}NO_2$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.82; H, 8.01; N, 5.88.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.00 – 6.45 (m, 3H, **H2',H5',H6'**), 4.70 (b.s, 1H, **NH**), 4.09 (q, *J* = 7.0 Hz, 2H, $OC\mathbf{H_2}CH_3$), 3.86 (s, 3H, $OC\mathbf{H_3}$), 3.85 (s, 3H, $OC\mathbf{H_3}$), 3.39 (q, *J* = 6.6 Hz, 2H, **H1**), 2.74 (t, *J* = 7.0 Hz, 2H, **H2**), 1.21 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H_3}$).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 156.7 (**C**O), 149.0, 147.7 (2x**C**-OCH_3), 131.4 (**C1'**), 120.7 (**C6**'), 111.9, 111.4 (**C2', C5'**), 60.8 ($OC\mathbf{H_2}CH_3$), 56.0, 55.9 (2x$OC\mathbf{H_3}$), 42.3 (**C1**), 35.8 (**C2**), 14.8 ($OCH_2\mathbf{C}H_3$).

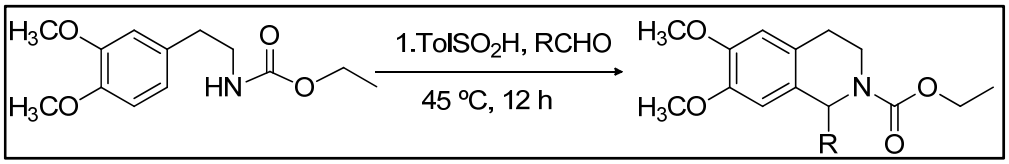
5.1.3. Synthesis of *p*-Toluene Sulfinic Acid 4[179].



A solution of sodium *p*-toluenesulfinate hydrate (5.0 g, 0.02 mmol) in H_2O (25 mL) was added diethyl ether (25.0 mL) and HCl 37% (1.80 mL) and the reaction was stirred during 1 h at room temperature. The organic layer was extracted with diethyl ether (1x 20 mL) and was dried over anhydrous Na_2SO_4 and filtered. The half solvent was evaporated under reduced pressure and after the addition of petroleum ether (20 mL) was obtained *p*-toluene sulfinic acid (2.96 g, 0.019 mmol) 95% yield as a white solid was filtered and kept in the freeze for one week (caution, hydroscopic solid).

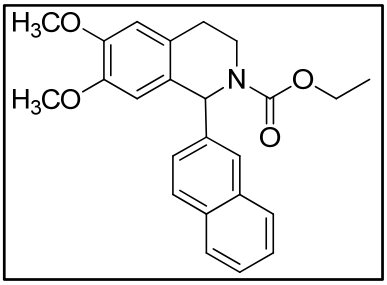
[179]Sisko, J.; Mellinger, M.; Sheldrake, P.; Baine, N. *Organic Syntheses*, **2004**, *10*, 692; **2000**, *77*, 198.

5.1.4. General procedure to obtain compounds 5a-5o.



A solution of compound **1** (1.0 eq) in DCM (56 eq) was added *p*-toluene sulfinic acid (1.0 eq), RCHO (1.1 eq–2.0 eq) the reaction mixture was heated to 45 ºC and was stirred for 12 h. Then the reaction was poured into 50 mL of a saturated aqueous solution of $NaHCO_3$ and extracted with DCM (3x 20 mL), the organic layer was dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure, and the mixture was purified by flash column cromatography using a mixture of petroleum ether:diethyl ether as eluent.

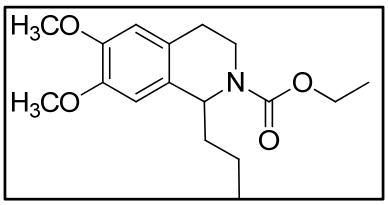
5.1.4.1. Synthesis and characterization of 1-(6,7-dimethoxy-1-(naphthalen-2-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)propan-1-one 5a.



Obtained according to the general procedure **4.1.4** using compound **2** (0.2 g, 0.84 mmol) as starting material, *p*-toluene sulfinic acid (0.13 g, 0.84 mmol), 2-naphthaldehyde (0.14 g, 0.92 mmol) and DCM (3.0 mL) as solvent. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **5a** (0.32 g, 0.84 mmol) as a clear brown oil in 99% yield; **IR (NaCl) ν_{max}** 2930, 2351, 1693 cm^{-1}; **Analysis**: Calcd. for $C_{24}H_{25}N$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.67; H, 6.85; N, 3.61; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.92 – 7.66* (m, 3H, **H1', H3', H4'**), 7.57-7.51* (m, 2H, **, H6', H7'**), 7.43-7.26* (m, 2H, **H8', H9'**), 6.72** (s, 1H, **H5'**), 6.57** (s, 1H, **H8'**), 4.24 (q, *J* = 6.4 Hz, 2H, OCH_2CH_3), 4.10-4.02 (m, 6.6 Hz, 1H, **H3**), 3.89 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.30 – 3.11 (m, 1H, **H3**), 3.11 – 2.86 (m, 1H, **H4**), 2.79-2.62 (m, 1H, **H4**), 1.47-1.13 (m, 3H, OCH_2CH_3).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 155.9 (**CO**), 148.6, 147.9 (2x**C**-OCH_3), 140.6 (**C2'**), 133.4, 133.2 (***C4a', *C8a'**), 128.6, 128.5, 128.0, 127.9, 127.7 (***C1', *C3', *C4', *C5', *C6', *C7', *C8'**), 127.2, 127.2 (***C4a, *C8a**),

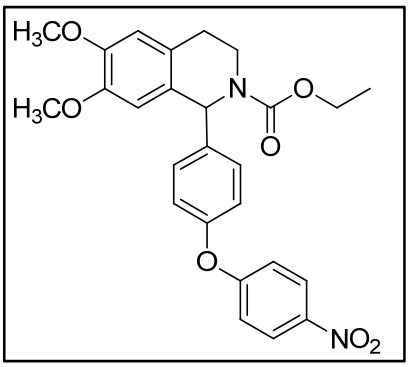
126.6, 126.5 (***C1', *C3', *C4', *C5', *C6', *C7', *C8'**), 111.8, 111.6 (***C5, *C8**), 62.0 (OCH_2CH_3), 57.7 (**C1**), 56.3 (2xOCH_3), 38.1 (**C3**), 28.5 (**C4**), 15.2 (OCH_2CH_3).

5.1.4.2. Synthesis and characterization of 1-(6,7-dimethoxy-1-propyl-3,4-dihydroisoquinolin-2(1*H*)-yl)propan-1-one 5b.



Obtained according to the general procedure **4.1.4** using compound **2** (0.2 g, 0.84 mmol) as starting material, *p*-toluene sulfinic acid (0.13 g, 0.84 mmol), butyraldehyde (0.1 g, 1.4 mmol) and DCM (3.0 mL) as solvent. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **5b** (0.22 g, 0.75 mmol) as a clear brown oil in 89% yield; **IR (NaCl) ν_{max}** 2934, 2350, 1695 cm^{-1}; **Analysis**: Calcd. for $C_{17}H_{25}NO_4$: C, 70.07; H, 8.65; N, 4.81 Found: C, 69.99; H, 8.77; N, 4.81; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.57 (s, 2H, **H5, H8**), 5.14 – 4.95 (m, 3H, **H1**), 4.16 (m, 2H, OCH_2CH_3, **H3**), 3.85 (bs, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.34-3.10 (m, 1H, **H3**), 2.98-2.75 (m, 3H, **H4**), 2.60 (dd, *J* = 15.9, 3.1 Hz, 1H, **H4**), 1.71 – 1.57 (m, 2H, **H1'**), 1.46 – 1.39 (m, 2H, **H2'**), 1.26 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 0.95 (t, *J* = 7.3 Hz, 3H, CH_3).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 156.0 (**CO**), 147.4 (2x**C**-OCH_3), 130.4, 130.0, 126.2, 125.8 (**C4a, C8a**), 111.6, 111.4, 110.2, 109.9 (**C5, C8**), 61.4 (OCH_2CH_3), 56.1 , 55.9 (2xOCH_3), 54.2, 54.1 (**C1**), 39.2, 39.0 (**C1'**), 38.0, 37.2 (**C3**), 28.1, 27.9 (**C4**), 19.8, 19.6 (**C2'**), 14.8 (OCH_2CH_3), 14.1 (**C3'**).

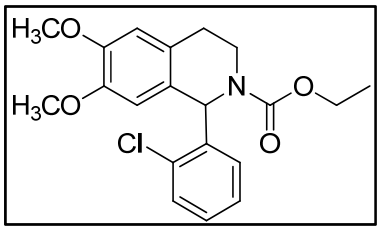
5.1.4.3. Synthesis and characterization of 1-(6,7-dimethoxy-1-(4-(4-nitrophenoxy)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)propan-1-one 5c.



Obtained according to the general procedure **4.1.4** using compound **2** (0.2 g, 0.84 mmol) as starting material, *p*-toluene sulfinic acid (0.13 g, 0.84 mmol), 4-(4-nitrophenoxy) benzaldehyde (0.22 g, 0.92 mmol) and DCM (3.0 mL) as solvent. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **5c** (0.34 g, 0.74mmol) as a clear yellow oil in 88% yield; **IR (NaCl)**

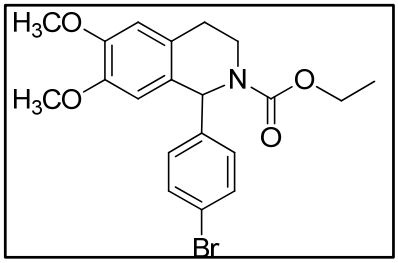
ν_{max} 2931, 2353, 1795, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{26}H_{26}N_2O_8$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.40; H, 5.70; N, 5.97; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.14 – 7.99 (m, 2H, **H3'',H5''**), 7.24 (d, *J* = 8.3 Hz, 2H, **H2', H6'**), 7.02 – 6.84 (m, 4H, **H3', H5', H2'', H6''**), 6.62 (s, 1H, ***H5, *H8**), 6.45 (s, 2H, ***H5, *H8**), 6.31 (s, 1H, **H1**), 4.31 – 3.91 (m, 3H, OCH_2CH_3, **H3**), 3.79 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.09 (m, 1H, **H3**), 2.99 – 2.75 (m, 1H, **H4**), 2.75 – 2.55 (m, 2H, **H4**), 1.35 – 1.15 (m, 3H, OCH_2CH_3).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 162.9 (**C4'**), 155.3 (**C1''**), 153.7 (**CO**), 148.0, 147.3 (2x**C**-OCH_3), 142.4, 139.8 (**C1', C4''**), 130.2 (**C2', C6'**), 127.0, 126.3 (**C4a, C8a**), 125.7 (**C3'', C5''**), 119.9, 117.0 (**C3', C5', C2'',C6''**), 111.2, 110.8 (**C5, C8**), 61.4 (OCH_2CH_3), 56.3 (**C1**), 55.8, 55.6 (2xOCH_3), 37.5 (**C3**), 27.7 (**C4**), 14.6 (OCH_2CH_3).

5.1.4.4. Synthesis and characterization of 1-(1-(2-chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propan-1-one 5d.



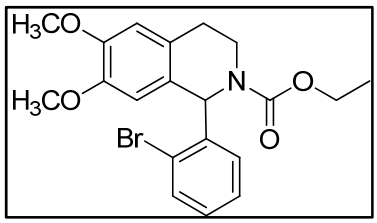
Obtained according to the general procedure **4.1.4** using compound **2** (0.2 g, 0.84 mmol), *p*-toluene sulfinic acid (0.13 g, 0.84 mmol), 2-Chlorobenzaldehyde (0.13 g, 0.92 mmol) as starting material and DCM (3.0 mL) as solvent. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **5d** (0.22 g, 0.61 mmol) as a yellow solid in 75% yield. **Mp** 88 – 90ºC; **IR(NaCl) ν_{max}** 2940, 2334, 1685 cm^{-1}; **Analysis**: Calcd. for $C_{20}H_{22}NO_4$: C, 66.75; H, 6.16; N, 3.89 Found: C, 66.75; H, 6.16; N, 3.89; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.4, 1.9 Hz, 1H, **H5'**), 7.21 – 7.01 (m, 2H, **H3', H4'**), 6.95 (d, *J* = 5.1 Hz, 1H, **H6'**), 6.62 (s, 1H, **H5**), 6.51 (s, 1H, **H1**), 6.46 (s, 1H, **H8**), 4.24 – 3.96 (m, 3H, OCH_2CH_3, **H3**), 3.82 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.28 (t, *J* = 10.0 Hz, 1H, **H3**), 2.94 (ddd, *J* = 16.6, 11.1, 5.7 Hz, 1H, **H4**), 2.71 (d, *J* = 16.0 Hz, 1H, **H4**), 1.17 (t, *J* = 6.9 Hz, 3H, OCH_2CH_3).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 155.6 (**C**O), 148.0, 147.6 (**C**-OCH_3), 141.1 (**C1'**), 133.9 (**C2'**), 130.2 (**C6'**), 129.7 (**C5'**), 128.5* (**C3'**), 126.9, 126.8 (**C4a, C8a**), 126.6* (**C4'**), 111.2 (**C5**), 110.4 (**C8**), 61.4 (OCH_2CH_3), 55.7 (2xOCH_3), 54.9 (**C1**), 38.8 (**C3**), 27.9(**C4**), 14.4(OCH_2CH_3).

5.1.4.5. Synthesis and characterization of 1-(1-(4-bromophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propan-1-one 5e.



Obtained according to the general procedure **4.1.4** using compound **2** (0.2 g, 0.84 mmol), *p*-toluene sulfinic acid (0.13 g, 0.84 mmol), 4-bromobenzaldehyde (0.17 g, 0.92 mmol) as starting material and DCM (3.0 mL) as solvent. Purification by flash column chromatography on silica gel using 1:9 Petroleum ether:diethyl ether as eluent afforded product **5e** (0.26 g, 0.63 mmol) as a clean yellow oil in 75% yield. **IR(NaCl) ν_{max}** 2930, 2345, 1675cm^{-1};**Analysis**: Calcd**.** for $C_{20}H_{22}NO_4$: C, 59.42; H, 5.48; N, 3.46. Found: C, 59.23; H, 5.31; N, 3.26. ;**^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.38 – 7.29* (m, 2H, **H2', H3'**), 7.07 – 6.98 (m, 2H**, H5', H6'**), 6.62 (s, 1H, **H5**), 6.41 (s, 1H, **H8**), 6.26 (bs, 1H, **H1**), 4.13 (q, *J* = 7.0 Hz, 2H, O**CH_2**CH_3), 4.08 – 3.89 (m, 1H, **H3**), 3.81 (s, 3H, O**CH_3**), 3.68 (s, 3H, O**CH_3**), 3.14 – 2.97 (m, 1H, **H3**), 2.97 – 2.78 (m, 1H, **H4**), 2.59 (dd, *J* = 10.8, 8.1 Hz, 1H, **H4**), 1.32 – 1.19 (t, *J* = 7.0Hz, 3H,OCH_2**CH_3**);**^{13}C NMR** (63 MHz, $CDCl_3$) δ 155.2 (**CO**), 148.0, 147.4 (**C6, C7**), 141.6 (**C1'**), 131.2, 130.1 (**C2', C3', C5', C6'**), 127.0, 126.1 (**C4a, C8a**), 121.3 (**C5'**), 111.2 (**C5**),, 110.7 (**C8**), 61.4 (OCH_2CH_3), 56.4 (**C1**), 55.8, 55.7 (2xO**CH_3**), 37.5 (**C3**), 27.8 (**C4**), 14.6 (OCH_2CH_3).

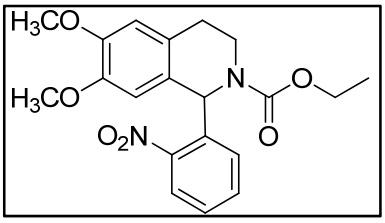
5.1.4.6. Synthesis and characterization of 1-(1-(2-bromophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propan-1-one 5f.



Obtained according to the general procedure **4.1.4** using compound **2** (0.2 g, 0.84 mmol) as starting material, *p*-toluene sulfinic acid (0.13 g, 0.84 mmol), 2-bromobenzaldehyde (0.17 g, 0.92 mmol) and DCM (3.0 mL) as solvent. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **2f** (0.31 g, 0.75 mmol) as a yellow oil in 90% yield. **IR (NaCl) ν_{max}** 2934, 2350, 1695 cm^{-1}; **Analysis:** Calcd. for $C_{20}H_{22}NO_4$: C, 59.42; H, 5.48; N, 3.46. Found: C, 59.37; H, 5.55; N, 3.39.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.9, 1.4 Hz, 1H, **H5'**), 7.21-6.90 (m, 3H, **H2', H3', H5'**), 6.62 (s, 1H, **H5**), 6.50 (s, 1H, **H8**), 6.43 (s, 1H, **H1**), 4.10 (m, 3H, O**CH_2**CH_3, **H3**), 3.82 (s, 3H, O**CH_3**), 3.67 (s, 3H, O**CH_3**), 3.46 – 3.21 (m, 1H, **H3**), 3.00-2.85 (m, 1H, **H4**), 2.73 (m, 1H, **H4**), 1.16 (t, *J* =

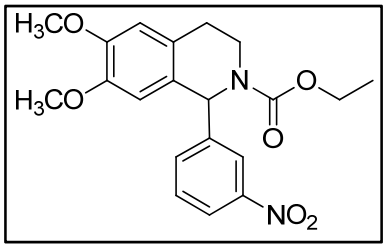
7.0 Hz, 3H, OCH_2CH_3).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 155.8 (**C**O), 147.9, 147.6 (2x**C**-OCH_3), 143.0 (**C1'**), 133.0 (**C5'**), 129.9, 128.7, 127.4 (**C3', C4', C6'**), 127.1, 126.6 (**C4a, C8a**), 124.1 (**C2'**), 111.2 (**C5**), 110.4 (**C8**), 61.5 (OCH_2CH_3), 57.2 (**C1**), 55.8 (2xOCH_3), 39.3 (**C3**), 28.1 (**C4**), 14.5 (OCH_2CH_3).

5.1.4.7. Synthesis and characterization of 1-(6,7-dimethoxy-1-(2-nitrophenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)propan-1-one 5g.



Obtained according to the general procedure **4.1.4** using compound **2** (0.2 g, 0.84 mmol) as starting material, *p*-toluene sulfinic acid (0.13 g, 0.84 mmol), 2-nitrobenzaldehyde (0.14 g, 0.92 mmol) and DCM (3.0 mL) as solvent. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **5g** (0.22 g, 0.58 mmol) as a yellow solid in 69% yield. **Mp** 110 – 112ºC; **IR(NaCl) ν_{max}** 2934, 2350, 1695, 1634 cm^{-1}.**Analysis**: Calcd. for $C_{20}H_{22}N_2O_6$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.72; H, 5.82; N, 7.51; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 7.9, 1.4 Hz, 1H, **H5'**), 7.45 – 7.28 (m, 2H, **H3', H4'**), 7.21 (d, *J* = 7.4 Hz, 1H, **H6'**), 6.69 (s, 1H, **H1**), 6.65 (s, 1H, **H5**), 6.57 (s, 1H, **H8**), 4.24 (bs, 1H, **H3**), 4.16 – 3.94 (m, 2H, OCH_2CH_3), 3.83 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.32 (ddd, *J* = 13.4, 10.8, 4.2 Hz, 1H, **H3**), 3.01 – 2.84 (m, 1H, **H4**), 2.77 (dt, *J* = 16.0, 3.6 Hz, 1H, **H4**), 1.13 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).; **^{13}C NMR** (63 MHz, **$CDCl_3$**) δ 155.3 (CO), 150.2 (**C2'**), 148.2, 148.0 (2x**C**-OCH_3), 137.9 (**C1'**), 132.4* (**C3'**), 130.2 (**C6'**), 128.1* (**C4'**), 126.7 (**C4a**), 126.1 (**C8a**), 123.7 (**C5'**), 111.0 (**C5**), 110.7 (**C8**), 61.8 (OCH_2CH_3), 55.9, 55.8 (2xOCH_3), 51.3 (**C1**), 38.4 (**C3**), 28.2 (**C4**), 14.3 (OCH_2CH_3).

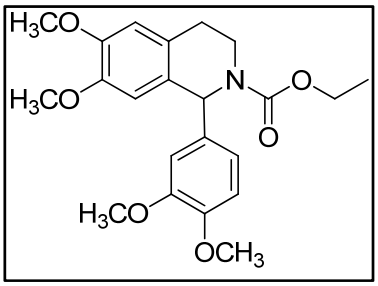
5.1.4.8. Synthesis and characterization of 1-(6,7-dimethoxy-1-(3-nitrophenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)propan-1-one 5h.



Obtained according to the general procedure **4.1.4** using compound **2** (0.2 g, 0.84 mmol) as starting material, *p*-toluene sulfinic acid (0.13 g, 0.84 mmol), 3-nitrobenzaldehyde (0.14 g, 0.92 mmol) and DCM (3.0 mL) as solvent. Purification by flash column chromatography on silica gel using 1:9 petroleum

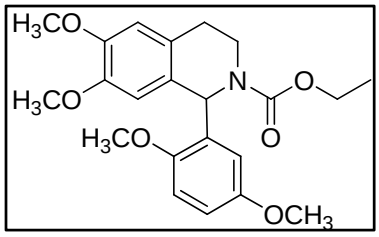
ether:diethyl ether as eluent afforded product **5h** (0.22 g, 0.58 mmol) as a yellow oil in 83% yield; **IR (NaCl) ν_{max}** 2941, 2345, 1695, 1610 cm^{-1}; **Analysis**: Calcd. for $C_{20}H_{22}N_2O_6$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.70; H, 5.81; N, 7.51; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.02 – 7.90 (m, 2H, **H2', H4'**), 7.60 (bs, 1H, **H5'**), 7.40 (t, *J* = 8.0 Hz, 1H, **H6'**), 6.65 (s, 1H, **H5**), 6.42 (s, 1H, **H8**), 6.34 (b.s, 1H, **H1**) 4.14 (q, 2H, OCH_2CH_3),4.05- 3.90 (m, 1H, **H3**), 3.82 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.17- 2.90 (m, 1H, **H3**), 2.98 – 2.80 (m, 1H, **H4**), 2.75 – 2.57 (m, 1H, **H4**), 1.33 – 1.17 (m, 3H, OCH_2CH_3).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 155.5 (**C**O), 148.3, 148.1 (**C6, C7**), 147.61 (**C3'**), 144.8 (**C1'**), 134.5 , 129.1, 127.1, 125.2, 123.1, 122.4 (**C2', C4', C5', C6'**), 111.4 (**C5**), 110.6 (**C8**), 61.7 (OCH_2CH_3), 56.4 (**C1**), 55.8, 55.7 (2xOCH_3), 38.0 (**C3**), 27.7 (**C4**), 14.5 (OCH_2CH_3).

5.1.4.9. Synthesis and characterization of ethyl 1-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 5i.



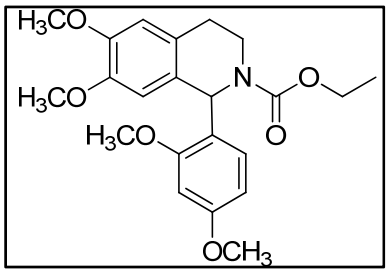
Obtained according to the general procedure 1.6 using compound **2** (0.2 g, 0.84 mmol) as starting material, *p*-toluene sulfinic acid (0.13 g, 0.84 mmol), 3,4-dimethoxibenzaldehyde (0.21 g, 1.30 mmol) and DCM (3.0 mL) as solvent, the reaction was heated to 45ºC and stirred for 20 h. Purification by flash column chromatography on silica gel using 2:8 petroleum ether:diethyl ether as eluent afforded product **2i** (0.29 g, 0.74 mmol) as a yellow solid in 88% yield; **Mp** 110–112ºC; **IR (NaCl) ν_{max}** 2933, 2351, 1695 cm^{-1}; **Analysis**: Calcd. for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.80; H, 6.82; N, 3.44; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.87 (bs, 1H, **H2'**), 6.69 (d, *J* = 8.3 Hz, 1H, **H5'**), 6.62 (s, 1H, **H5**), 6.59 (dd, *J* = 8.4, 1.9 Hz, 1H, **H6'**), 6.45 (s, 1H, **H8**), 6.27 (bs, 1H, **H9**), 4.15 (dd, *J* = 14.1, 7.0 Hz, 2H, OCH_2CH_3), 4.08 – 3.94 (m, 1H, **H3**), 3.83 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.07 (td, *J* = 12.3, 3.8 Hz, 1H, **H3**), 2.98 – 2.80 (m, 1H, **H4**), 2.61 (m, 1H, **H4**), 1.26 (s, 3H, OCH_2CH_3).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 155.3 (**C**O), 148.7, 148.3, 147.9, 147.3 (4x**C**-OCH_3), 135.3 (**C1'**), 127.0, 126.9 (**C4a, C8a**), 120.9 (**C6'**), 111.9 (**C2'**), 111.1, 110.9 (**C5, C8**), 110.4 (**C5'**), 61.3 (OCH_2CH_3), 56.7 (**C1**), 55.8, 55.8, 55.7 (4x OCH_3), 37.2 (**C3**), 28.0 (**C4**), 14.7 (OCH_2CH_3).

5.1.4.10. Synthesis and characterization of ethyl 1-(2,5-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 5j.



Obtained according to the general procedure 1.6 using compound 2 (0.2 g, 0.84 mmol) as starting material, *p*-toluene sulfinic acid (0.13 g, 0.84 mmol), 2,5-dimethoxibenzaldehyde (0.21 g, 1.30 mmol) and DCM (3.0 mL) as solvent, the reaction was heated to 45 ºC and stirred for 20 h. Purification by flash column chromatography on silica gel using 2:8 petroleum ether:diethyl ether as eluent afforded product 5j (0.26 g, 0.66 mmol) as a clear yellow oil in 79% yield. **IR(NaCl) ν_{max}** 2934, 2350, 1695 cm^{-1}; **Analysis**: Calcd. for $C_{22}H_{27}N$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.77; H, 6.71; N, 3.53; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.8 Hz, 1H, **H3'**), 6.71 (dd, *J* = 8.9, 2.9 Hz, 1H, **H4'**), 6.61 (s, 1H, **H4**), 6.54* (s, 1H, **H1**), 6.46 (s, 1H, **H8**), 6.46* (s, 1H, **H6'**), 4.21 – 3.90 (m, 3H, O**CH$_2$**CH_3, **H3**), 3.84 (s, 3H, O**CH$_3$**), 3.80 (s, 3H, O**CH$_3$**), 3.72 (s, 3H, O**CH$_3$**), 3.65 (s, 3H, O**CH$_3$**), 3.39 (dd, *J* = 17.0, 3.2 Hz, 1H, **H3**), 3.00 - 2.81 (m, 1H, **H4**), 2.71 (dt, *J* = 16.0, 3.9 Hz, 1H, **H4**), 1.26 – 1.20 (m, 3H, OCH_2**CH$_3$**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 155.6 (**C**O), 153.1, 151.6, 147.8, 147.4 (4x **C**-OCH_3), 132.9 (**C1'**), 127.7, 127.0 (**C4a, C8a**), 116.8, 111.9, 111.8, 111.2, 110.7 (**C4, C8, C3', C4', C6'**), 61.3 (OCH_2CH_3), 56.1 (**C1**), 55.8, 55.8, 55.6, 52.8 (4xOCH_3), 38.7 (**C3**), 27.9 (**C4**), 14.7 (OCH_2**C**H_3).

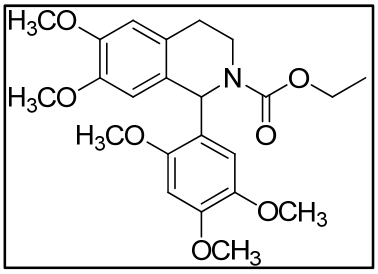
5.1.4.11. Synthesis and characterization of ethyl 1-(2,4-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 5k.



Obtained according to the general procedure 4.1.4 using compound 2 (0.2 g, 0.84 mmol) as starting material, *p*-toluene sulfinic acid (0.13 g, 0.84 mmol), 2,4-dimethoxibenzaldehyde (0.35 g, 2.10 mmol) and DCM (3.0 mL) as solvent, the reaction was heated to 45 ºC and stirred for 20 h. Purification by flash column chromatography on silica gel using 2:8 petroleum ether:diethyl ether as eluent afforded product 5k (0.15 g, 0.39 mmol) as a clear yellow oil in 41% yield; **IR (NaCl) ν_{max}** 2934, 2350 cm^{-1}; **Analysis**: Calcd. for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.90; H, 6.71; N, 3.30.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.71 (d, J = 8.4 Hz, 1H, **H6'**), 6.61 (s, 1H, **H5**), 6.48 (s, 1H, **H8**), 6.44 (d, J = 2.4 Hz, 2H, **H3'**),

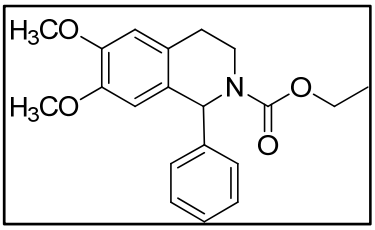
6.30 (dd, J = 8.4, 2.4 Hz, 1H, **H5'**), 4.25-3.95 (m, 3H, OC**H**$_2$CH$_3$, **H3**), 3.83 (s, 3H, OC**H**$_3$), 3.83 (s, 3H, OC**H**$_3$), 3.73 (s, 3H, OC**H**$_3$), 3.70 (s, 3H, OC**H**$_3$), 3.33- 3.15 (m, 1H, **H3**), 3.06 – 2.79 (m, 1H, **H4**), 2.74 – 2.55 (m, 1H, **H4**), 1.24 (t, J = 7.1 Hz, 3H, OCH$_2$C**H**$_3$).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 160.2 (**C**O), 158.4, 155.5 (**C2', C4'**), 147.7, 147.3 (**C6, C7**), 130.7 (**C6'**), 128.2 (**C8a**), 127.1 (**C4a**), 123.7 (**C1'**), 111.1 (**C5**), 110.7 (**C8**), 103.4 (**C5'**), 98.5 (**C3'**), 61.2 (O**C**H$_2$CH$_3$), 55.8 , 55.4, 55.2 (4xO**C**H$_3$), 52.4 (**C1**), 38.1 (**C3**), 27.9 (**C4**), 14.7 (OCH$_2$**C**H$_3$).

5.1.4.12. Synthesis and characterization of ethyl 6,7-dimethoxy-1-(2,4,5-trimethoxyphenyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 5m.



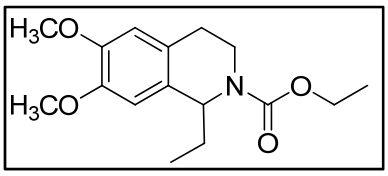
Obtained according to the general procedure **4.1.4** using compound **2** (0.2 g, 0.84 mmol) as starting material, *p*-toluene sulfinic acid (0.13 g, 0.84 mmol), 2,4,5-trimethoxibenzaldehyde (0.41 g, 2.10 mmol) and DCM (3.0 mL) as solvent, the reaction was heated to 45 ºC and stirred for 24 h. Purification by flash column chromatography on silica gel using 2:8 petroleum ether:diethyl ether as eluent afforded product **2m** (0.22 g, 0.48 mmol) as a yellow solid in 57% yield; **IR (NaCl) ν_{max}** 2934, 2350, 1695 cm^{-1}; **Analysis**: Calcd. for $C_{23}H_{29}N$: C, 64.02; H, 6.77; N, 3.25. Found: C, 64.11; H, 6.81; N, 3.33; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.56 (s, 1H, **H5**), 6.48 (s, 1H, **H3'**), 6.45 (s, 1H, **H8**), 6.40 (s, 1H, **H6**), 6.38 (s, 1H, **H1**), 4.16- 3.92 (m, 3H, OC**H**$_2$CH$_3$, **H3**), 3.79 (s, 3H, OC**H**$_3$), 3.77 (s, 3H, OC**H**$_3$), 3.73 (s, 3H, OC**H**$_3$), 3.65 (s, 3H, OC**H**$_3$), 3.59 (s, 3H, OC**H**$_3$), 3.37 – 3.19 (m, 1H, **H3**), 2.86 (m, 1H, **H4**), 2.64 (m, 1H, **H4**), 1.17 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 155.3 (**C**O), 151.8, 149.0, 147.5 (**C2', C4', C5'**), 147.2, 142.2 (**C6, C7**), 128.0 (**C8a**), 126.8 (**C4a**), 123.0 (**C1'**), 114.3 (**C6'**), 111.0 (**C5**), 110.5 (**C8**), 97.7 (**C3'**), 61.0 (O**C**H$_2$CH$_3$), 56.6, 56.4, 55.9, 55.7, 55.6 (4xO**C**H$_3$), 52.5 (**C1**), 38.5 (**C3**), 27.9 (**C4**), 14.5 (OCH$_2$**C**H$_3$).

5.1.4.13. Synthesis and characterization of ethyl 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 5n.



Obtained according to the general procedure **4.1.4** using compound **2** (0.2 g, 0.84 mmol) as starting material, *p*-toluene sulfinic acid (0.13 g, 0.84 mmol), benzaldehyde (1.0 mL, 0.98 mmol, 1.17 eq) and DCM (3.0 mL) as solvent. Purification by flash column chromatography on silica gel using 2:8 petroleum ether:diethyl ether as eluent afforded product **5n** (0.16 g, 0.47 mmol) as a yellow oil in 56% yield; **IR (NaCl)** ν_{max} 2931, 2341 cm^{-1}; **Analysis**: Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.43; H, 6.76; N, 4.23.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.30 (s, 5H, **H2', H3', H4', H5', H6'**), 6.72 (s, 1H, **H5**), 6.54 (s, 1H, **H8**), 6.43 (bs, 1H, **H1**), 4.37 – 4.00 (m, 3H, OCH_2CH_3, **H3**), 3.91 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.28 – 3.09 (m, 1H, **H3**), 3.09 – 2.82 (m, 1H, **H4**), 2.71 (d, *J* = 15.1 Hz, 1H, **H4**), 1.31 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 155.3 (**C**O), 147.8, 147.2 (**C6, C7**), 142.5 (**C1'**), 128.4, 128.0, 127.2 (**C2', C3', C4', C5', C6'**), 126.9, 126.7(**C4a, C8a**), 111.1 (**C5**), 110.8 (**C8**), 61.3 (OCH_2CH_3), 56.9 (**C1**), 55.7, 55.6 (OCH_3), 37.4 (**C3**), 27.8 (**C4**), 14.6 (OCH_2CH_3).

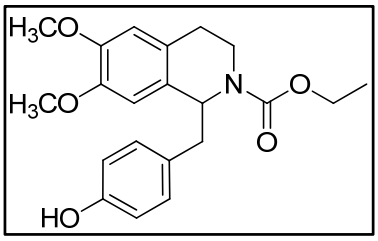
5.1.4.14. Synthesis and characterization of ethyl 1-ethyl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 5o.



Obtained according to the general procedure **4.1.4** using compound **2** (0.2 g, 0.84 mmol) as starting material, *p*-toluene sulfinic acid (0.13 g, 0.84 mmol), propanaldehyde (1.0 mL, 1.37 mmol) and DCM (3.0 mL) as solvent. Purification by flash column chromatography on silica gel using 7:3 petroleum ether:diethyl ether as eluent afforded product **5o** (0.16 g, 0.47 mmol) as a brown oil in 97% yield; **IR (NaCl)** ν_{max} 2961**,** 2934, 2350, 1695 cm^{-1}; **Analysis**: Calcd. for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.63; H, 7.95; N, 4.67; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.54 (s, 2H, **H5, H8**), 5.04 - 4.85 (m, 1H, **H1**), 4.27 – 3.90 (m, 3H, OCH_2CH_3, **H3**), 3.80 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.29 – 3.05 (m, 1H, **H3**), 2.96 – 2.68 (m, 1H, **H4**), 2.57 (m, 1H, **H4**), 1.82 – 1.65 (m, 2H, **H1'**), 1.22 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 0.92 (t, *J* = 7.4 Hz, 3H, **H2'**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 155.9 (**C**O), 147.5, 147.2 (2x**C**-OCH_3), 130.0, 129.7, 126.0, 125.7 (**C4a, C8a**), 111.4, 111.3,

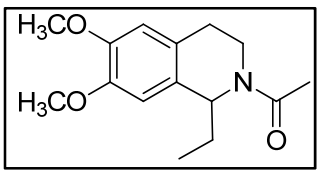
110.0, 109.8 (**C5, C8**), 61.2 (OCH_2CH_3), 55.9, 55.8 (OCH_3), 55.5 (**C1**), 37.9, 37.1 (**C3**), 29.7, 29.4 (**C1'**), 28.0, 27.8 (**C4**), 14.6 (OCH_2CH_3), 10.9 (**C2'**).

5.1.4.15. Synthesis and characterization of ethyl 1-(4-hydroxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 5p.



Obtained according to the general procedure **4.1.4** using compound **2** (0.1 g, 0.42 mmol) as starting material, *p*-toluene sulfinic acid (0.085 g, 0.54 mmol), 4-hydroxybenzaldehyde (0.063 g, 0.46 mmol) and DCM (1.5 mL) as solvent. Purification by flash column chromatography on silica gel using petroleum ether:diethyl ether as eluent afforded product **5p** (0.34 g, 0.90 mmol) as a clear yellow oil in 80% yield; **IR (NaCl) ν_{max}** 3330, 3014, 2935, 2836, 2361 cm^{-1}; **Analysis**: Calcd. for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 68.01; H, 6.72; N, 3.83; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.3 Hz, 2H, **H2'', H6''**), 6.72 (d, *J* = 8.3 Hz, 2H, **H3'', H4''**), 6.58 (s, 0.5H, **H5**), 6.60 (s, 0.5H, **H5**), 6.44, 6.28 (s, 1H, **H8**), 5,23 (t, *J* = 7.0 Hz, 0.5H, **H1**), 5.14 (t, *J* = 7.0 Hz, 0.5H, **H1**), 4.22 – 3.89 (m, 3H, OCH_2CH_3, **H3**), 3.84, 3.83 (s, 3H, OCH_3), 3.77, 3.65 (s, 3H, OCH_3), 3.46 – 3.24 (m, 1H, **H3**), 3.12 – 2.69 (m, 3H, **H4,** 2x**H1'**), 2.68 – 2.55 (m, 1H, **H4**), 1.23 (t, *J* = 8.3 Hz, 1.5H, OCH_2CH_3), 1.09 (t, *J* = 8.3 Hz, 1.5H, OCH_2CH_3).; **^{13}C** NMR (63 MHz, $CDCl_3$) δ 156.1, 155.9 (**CO**), 155.4, 155.3 (**C4''**), 147.8, 147.6, 147.2, 146.9 (2x**C**-OCH_3), 130.8, 130.7 (**C2'',C6''**), 129.5, 129.4 (**C1''**), 128.6, 128.3, 126.3, 126.0 (**C4a, C8a**), 115.2 (**C3'', C5''**), 111.5, 111.2 (**C5**), 110.6, 110.2 (**C8**), 61.7 (OCH_2CH_3), 56.4, 56.4, 55.9 (2xOCH_3), 55.8 (**C1**), 42.1, 41.9 (**C1'**), 38.9, 37.9 (**C3**), 28.1 (**C4**), 14.7, 14.5 (OCH_2CH_3).

5.1.4.16. Synthesis and characterization of 1-(1-ethyl-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethanone 6.

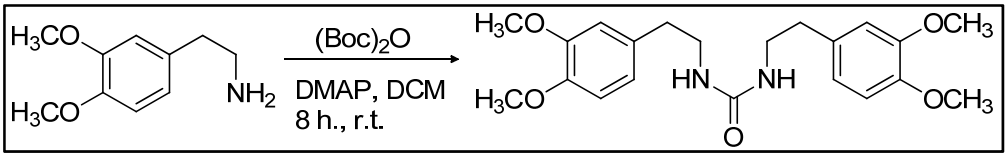


Obtained according to the general procedure **4.1.4** using compound **1** (0.1 g, 0.42 mmol) as starting material, *p*-toluene sulfinic acid (0.085 g, 0.54 mmol), propanaldehyde (2.0 mL, 2.7 mmol) and DCM (1.5 mL) as solvent, the reaction was heated to 45 ºC and stirred for 4 days. Purification by flash

column chromatography on silica gel using 5:5 Petroleum ether:diethyl ether as eluent afforded product **6** (0.34 g, 0.90 mmol) as a clear yellow oil in 45% yield; **IR (NaCl) ν_{max}** 2963, 2933, 2360 cm^{-1}; **Analysis**: Calcd. for $C_{15}H_{21}N$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.60; H, 8.01; N, 5.31; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.57 (m, 2H, **H5, H8**), 5.44 (dd, *J* = 8.4, 6.4 Hz, 0.5H, **H1**), 4.66 – 4.55 (m, 0.5H, **H1**), 4.03 – 3.67 (m, 7.5H, 2x O**C**$\mathbf{H_3}$, **H3**), 3.55 – 3.44 (m, 0.5H, **H3**), 3.04 – 2.58 (m, 2H, **H4**), 2.16 (s, 3H, CO-**C**$\mathbf{H_3}$), 1.92 – 1.66 (m, 2H, **H1'**), 0.99 (t, *J* = 7.4 Hz, 1.5H, **H2''**), 0.92 (t, *J* = 7.4 Hz, 1.5H, **H2''**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 169.8, 169.7 (**C**O), 148.0, 147.7, 147.6, 147.4 (2x**C**-OCH_3), 130.1, 129.1, 126.3, 125.1 (**C4a, C8a**), 111.6, 111.2, 110.4, 109.8 (**C5, C8**), 58.6 (**C1**), 56.1, 56.0, 55.9 (2xO**C**H_3), 53.4 (**C1**), 40.6 (**C3**), 35.2 (**C4**), 30.1, 29.4, 28.6, 27.6 (**C1'**), 21.8, 21.8 (CO**C**H_3) , 11.3, 11.0 (**C2'**).

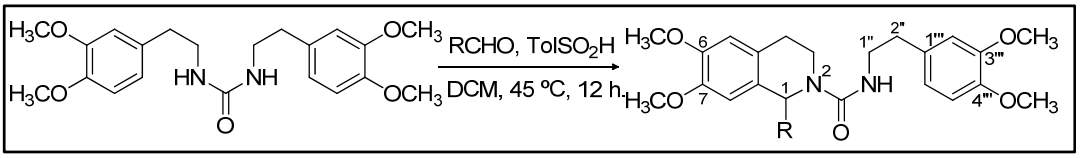
5.2. Synthesis of ureas derivative

5.2.1. Synthesis of 1,3-bis(3,4-dimethoxyphenethyl)urea 3.



To the compound commerciality available homoveratrilamine (3.0 g, 16.5 mmol) was added DMAP (2.0 g, 16.5 mmol), $(Boc)_2O$ (4 g, 18.0 mmol) and anhydrous DCM (10 mL) as solvent to room temperature for 8 h. The white solid was filtered and was washed with diethyl ether (2 x 10 mL) to give compound **7** (2.2 g, 5.7 mmol) as a white solid in 70% yield.; **Mp** 70 – 71 **ºC**; **IR (NaCl)** ν_{max} 3400, 2830, 1930 cm^{-1}; **Anal**. Calcd for $C_{21}H_{28}N_2$: C, 64.93; H, 7.27; N, 7.21 Found: C, 64.96; H, 7.36; N, 7.10.;^{1}**H NMR** (250 MHz, $CDCl_3$) δ 6.81 – 6.65 (m, 3H, **H2' ,H5', H6'**), 4.33 (s, 1H, N**H**), 3.83 (s, 12H, 4xO**CH$_3$**), 3.39 (t, *J* = 6.8 Hz, 2H, **H1**), 2.72 (t, *J* = 6.9 Hz, 2H, **H2**).;^{13}**C NMR** (63 MHz, $CDCl_3$) δ 158.1 (**C**O), 149.1, 147.7 (C-O**C**H$_3$), 131.7 (**C1'**), 120.8 , 112.0, 111.3 (**C2',C5', C6'**), 56.0, 55.9 (4xO**C**H$_3$), 41.8 (**C1**), 36.1 (**C2**).

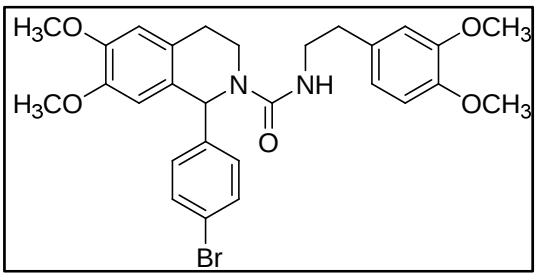
5.2.2. General procedure to obtain 6,7-dimethoxy-*N*'-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxamides 7a – 7j.



To a solution of compound **3** (1.0 equiv) in ethyl acetate (5.0 mL) the corresponding aryl or alkyl aldehyde (3 equiv.) and *p*-toluene sulfinic acid (1.1 – 3.0 equiv.) were added at 80 ºC for 12 h. The mixture was quenched with a saturate solution of Na_2HCO_3, extracted

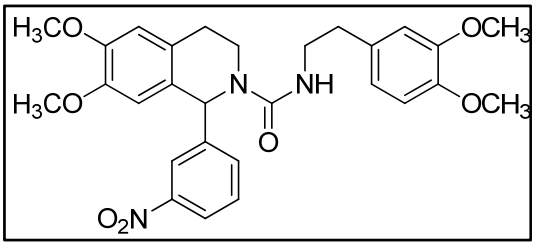
with DCM (2 x 30 mL) and concentrated under reduced pressure. The crude was purified by flash column chromatography using a mixture of diethyl ether:ethyl acetate to give the compounds **7a – 7j**.

5.2.2.1. Synthesis of 1-(4-bromophenyl)-6,7-dimethoxy-*N*'-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxamide 7a.



Obtained according to the general procedure **5.2.2** using compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluenesulfinic acid (0.098 g, 1.1 mmol, 2.2 equiv), 4-bromobenzaldehyde (0.28 g, 1.5 mmol) and AcOEt (5.0 mL) as solvent. Purification by flash column chromatography on silica gel using 8:2 diethyl ether:ethyl acetate as eluent afforded the product **7a** (0.071 g, 0.38 mmol) as a brown solid in 75 % yield; **Mp** 96 – 98 ºC; **IR (NaCl) ν_{max}** 3400, 2830, 1930 cm^{-1}; **Anal.** Cald. for $C_{28}H_{31}N_2$: C, 60.54; H, 5.63; N, 5.04. Found: C, 60.46; H, 5.67; N, 4.90; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.4 Hz, 2H, **H3', H5'**), 6.89 (d, *J* = 8.4 Hz, 2H, **H2', H6'**), 6.59* (d, *J* = 7.9 Hz, 1H, **H5**), 6.49* (d, *J* = 8.8 Hz, 3H, **H2''', H6''', H5**), 6.40 (s, 1H, **H8**), 6.18 (s, 1H, **H1**), 4.70 (t, *J* = 5.3 Hz, 1H, N**H**), 3.69 (s, 3H, O**CH$_3$**), 3.67 (s, 3H, O**CH$_3$**), 3.59 (s, 6H, 2xO**CH$_3$**) 3.42 –3.22 (m, 3H, **H1'', H3**), 3.18 – 3.05 (m, 1H, **H3**), 2.67 – 2.51 (m, 3H, **H2'', H4**), 2.52 – 2.32 (m, 1H, **H4**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 157.2 (N**C**ON), 148.7, 148.0, 147.3 (4xO**C**H$_3$), 141.9 (**C1'**), 131.6 (**C1'''**), 131.2 (**C3', C5'**), 129.5 (**C2', C6'**), 127.3, 126.8 (**C4a, C8a**), 121.0 (**C4'**), 120.5, 111.8, 111.1 (**C2''', C5''', C6'''**), 111.0 (**C5**), 110.8 (**C8**), 56.0, 55.8, 55.7 (4x O**C**H$_3$), 55.6 (**H1**), 42.1 (**C1''**), 39.1 (**C3**), 35.6 (**C2''**), 27.4 (**C4**).

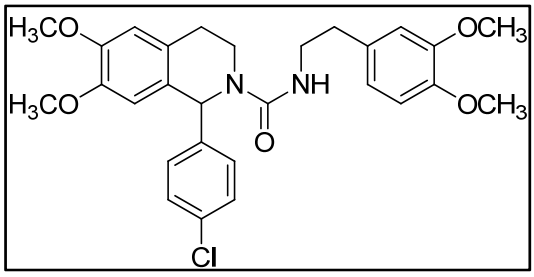
5.2.2.1. Synthesis of 6,7-dimethoxy-*N*'-(3,4-dimethoxyphenethyl)-1-(3-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxamide 7b.



Obtained according to the general procedure **5.2.2** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluenesulfinic acid (0.24 g, 1.53 mmol, 3 equiv), 3-nitrobenzaldehyde (0.23 g, 1.5

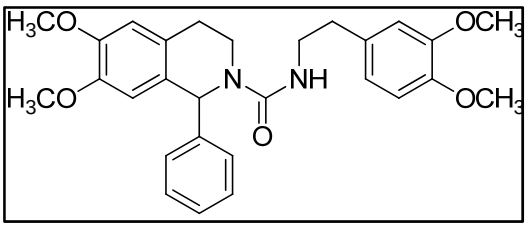
mmol) and AcOEt (5.0 mL) as solvent. Purification by flash column chromatography on silica gel using 8:2 diethyl ether:ethyl acetate as eluent afforded the product **7b** (0.23 g, 0.43 mmol) as a pale yellow solid in 85% yield; **Mp** 153 – 155 ºC; **IR (NaCl) ν_{max}** 3400, 2830, 1930, 1519, 1347 cm^{-1}; **Anal.** Calcd. for $C_{28}H_{31}N_3$: C, 64.48; H, 5.99; N, 8.06; Found: C, 64.46; H, 5.78; N, 7.90; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.06* (ddd, *J* = 8.1, 2.0, 0.9 Hz, 1H, **H6'**), 8.00* (dd, *J* = 2.2, 1.8 Hz, 1H, **H4'**), 7.59 (m, 1H, **H2'**), 7.42 (t, *J* = 7.9 Hz, 1H, **H5'**), 6.79 – 6.63 (m, 5H, **H2''', H5''', H6'''**), 6.51 (s, 1H, **H1**), 4.61 (t, *J* = 5.6 Hz, 1H, **NH**), 3.87 (s, 3H, **OCH_3**), 3.84 (s, 3H, **OCH_3**), 3.80 (s, 3H, **OCH_3**), 3.77 (s, 3H, **OCH_3**), 3.62 – 3.44 (m, 2H, **H1''**), 3.34 (t, *J* = 6.2 Hz, 2H, **H3**), 2.84 – 2.70 (m, 3H, **H2'', H4**), 2.61 (dt, *J* = 15.8, 5.7 Hz, 1H, **H4**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 157.4 (N**C**ON), 149.1, 148.6 (2x**C**-OCH_3), 148.4 (**C3'**), 147.9, 147.7 (2x**C**-OCH_3), 145.5 (**C1'**), 134.1 (**C2'**), 131.7 (**C1'''**), 129.3* (**C5'''**), 127.0 (**C4a, C8a**), 122.4, 122.3 (**C4'', C6''**), 120.7 (**C5''**), 112.0* (**C2'''**), 111.4, 111.4 (**C5, C8**), 111.0* (**C6'''**), 56.2, 56.1 (**OCH_3, C1**), 56.0, 55.9, 55.8 (3x**OCH_3**), 42.3 (**C1'**), 40.0 (**C3**), 35.8 (**C2''**), 27.6 (**C4**)

5.2.2.2. Synthesis of -(4-chlorophenyl)-6,7-dimethoxy-*N*'-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxamide 7c.



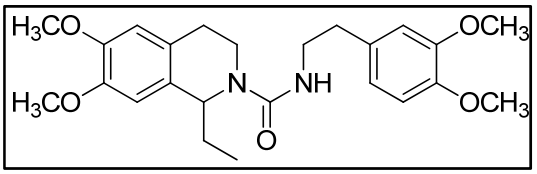
Obtained according to the general procedure **5.2.2** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluenesulfinic acid (0.24 g, 1.53 mmol, 3equiv), 4-chlorobenzaldehyde (0.23 g, 1.5 mmol) and AcOEt (5.0 mL) as solvent. Purification by flash column chromatography on silica gel using 8:2 diethyl ether:ethyl acetate as eluent afforded the product **7c** (0.22 g, 0.43 mmol) as a pale brown solid in 85 % yield; **Mp** 128 – 130 ºC; **IR (NaCl) ν_{max}** 3320, 2820, 1930 cm^{-1}; **Anal.** Calcd for $C_{28}H_{31}N_2$: C, 65.81; H, 6.11; N, 5.48; Found: C, 65.76; H, 5.97; N, 5.50; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 2H, **H3', H5'**), 7.10 (d, *J* = 8.5 Hz, 2H, **H2', H6'**), 6.76 (d, *J* = 8.6 Hz, 1H, **H6'''**), 6.17 – 6.65 (m, 2H, **H2''', H5'''**), 6.63 (s, 1H, H5), 6.55 (s, 1H, H8), 6.33 (s, 1H, H1), 4.58 (t, *J* = 5.6 Hz, 1H, NH), 3.85 (s, 3H, **OCH_3**), 3.84 (s, 3H, **OCH_3**), 3.77 (s, 3H, **OCH_3**), 3.76 (s, 3H, **OCH_3**), 3.60 – 3.21 (m, 4H, **H3, H1''**), 2.84 – 2.68 (m, 3H, **H4, H2''**), 2.60 (dt, *J* = 16.0, 5.1 Hz, 1H, **H4**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 157.3 (**C**O), 149.0, 148.2, 147.6, 147.6 (4x**C**-OCH_3), 141.5 (C1'), 133.0 (**C4'**), 131.8 (**C1'''**), 129.3 (**C2', C6'**), 128.4 (**C3', C5'**), 127.6 (**C8a**), 127.0 (**C4a**), 120.7 (**C5'''**), 112.0 (**C2'''**), 111.3 (**C6'''**), 111.2 (**C5**), 111.0 (**C8**), 56.2 (**C1**), 56.0, 55.9, 55.8 (4x OCH_3), 42.3 (**C1''**), 39.4 (**C3**), 35.8 (**C2''**), 27.7 (**C4**).

5.2.2.3. Synthesis of 6,7-dimethoxy-*N*'-(3,4-dimethoxyphenethyl)-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide 7d.



Obtained according to the general procedure **5.2.2** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluene sulfinic acid (0.24 g, 1.53 mmol, 3equiv.), benzaldehyde (0.16 g, 1.5 mmol) and AcOEt (5.0 mL) as solvent. Purification by flash column chromatography on silica gel using 8:2 diethyl ether: ethyl acetate as eluent afforded the product **7d** (0.11 g, 0.24 mmol) as a pale brown solid in 46 % yield; **Mp** 128 – 130 ºC; **IR (NaCl) ν_{max}** 3320, 2820, 1930 cm^{-1}. **Anal**. Calcd for $C_{28}H_{32}N_2$: C, 70.57; H, 6.77; N, 5.88. Found: C, 70.66; H, 6.60; N, 5.70.; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31 – 7.17 (m, 5H, **H2'**, **H3'**, **H4'**, **H5'**, **H6'**), 6.80 (d, *J* = 8.7 Hz, 1H, **H5'''**), 6.75 – 6.69 (m, 2H, **H2''', H6'''**), 6.67 (s, 1H, **H5**), 6.62 (s, 1H, **H8**), 6.31 (s, 1H, **H1**), 4.59 (t, *J* = 5.6 Hz, 1H, **NH**), 3.90 (s, 3H, OC**H$_3$**), 3.89 (s, 3H, OC**H$_3$**), 3.81 (s, 3H, OC**H$_3$**), 3.80 (s, 3H, OC**H$_3$**), 3.60 – 3.46 (m, 3H, **H1'', H3**), 3.46 – 3.32 (m, 1H, **H3**), 2.88 – 2.75 (m, 3H, **H2'', H4**), 2.67 (dt, *J* = 15.8, 5.1 Hz, 1H, **H4**).; ^{13}C NMR (63 MHz, $CDCl_3$) δ 157.5 (**CO**), 149.0, 148.1, 147.6, 147.5 (4x**C** – OCH_3), 143.0 (**C1'**), 132.0 (**C1'''**), 128.0 (**C3', C5'**), 128.0 (**C8a**), 127.8 (**C2', C6'**), 127.3 (**C4'**), 127.1 (**C4a**), 120.7, 112.0 (**C2''', C6'''**), 111.4 (**C5'''**), 111.2 (**C4, C8**), 57.1 (**C1**), 56.1, 56.0, 55.8 (**4xOCH$_3$**), 42.3 (**C1''**), 39.4 (**C3**), 35.8 (**C2''**), 27.8 (**C4**).

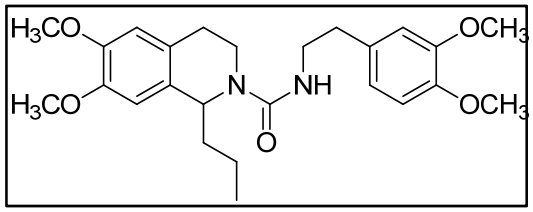
5.2.2.4. Synthesis of 1-ethyl-6,7-dimethoxy-*N*'-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxamide 7e.



Obtained according to the general procedure **5.2.2** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluenesulfinic acid (0.088 g, 0.56 mmol, 1.10 equiv), propionaldehyde (0.089 g, 1.53 mmol) and ethyl acetate (5.0 mL) as solvent. Purification by flash column chromatography on silica gel using 8:2 diethyl ether:ethyl acetate as eluent afforded the product **7e** (0.14 g, 0.33 mmol) as a brown oil in 64% yield; **IR (NaCl) ν_{max}** 3320, 2960, 1530 cm^{-1}; **Anal**. Calcd. for $C_{24}H_{32}N_2$: C, 67.27; H, 7.53; N, 6.54; Found: C, 67.26; H,

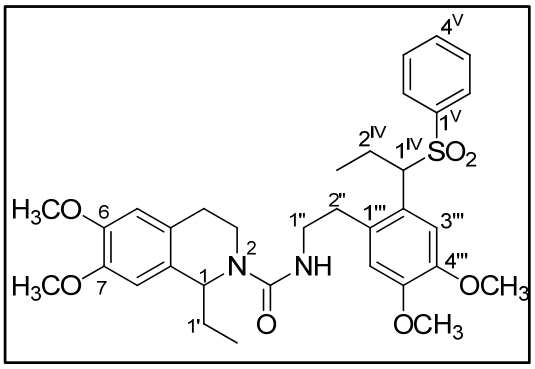
7.60; N, 6.44; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.73 (d, *J* = 8.7 Hz, 1H, **H5''**), 6.69 – 6.62 (m, 2H, **H2''', H6'''**), 6.54 (s, 1H, **H5**), 6.53 (s, 1H, **H8**), 4.77 (t, *J* = 7.1 Hz, 1H, **H1**), 4.60 (t, *J* = 5.6 Hz, 1H, **NH**), 3.80 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.73 – 3.57 (m, 1H, **H3**), 3.57 – 3.31 (m, 2H, **H1''**), 3.31 – 3.12 (m, 1H, **H3**), 2.84 – 2.69 (m, 3H, **H2'', H4**), 2.63 (dt, *J* = 15.7, 4.9 Hz, 1H, **H4**), 1.71 (tq, *J* = 13.8, 7.1 Hz, 2H, **H1'**), 0.89 (t, *J* = 7.4 Hz, 3H, **H2'**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 157.2 (**C**O), 148.8, 147.5, 147.4, 147.1 (4x**C**-OCH_3), 131.9 (**C1'''**), 130.1 (**C8a**), 126.1 (**C4a**), 120.6, 111.9 (**C2''', C6'''**), 111.2, 111.1 (**C5**, **C5'''**), 110.2 (**C8**), 56.0 (**C1**), 55.9, 55.8, 55.8, 55.7 (4x**OC**H_3), 42.2 (**C1''**), 38.3 (**C3**), 35.8 (**C2''**), 29.7 (**C1'**), 26.8 (**C4**), 11.2 (**C2'**).

5.2.2.5. Synthesis of 1-propyl-6,7-dimethoxy-*N'*-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxamide 7f.



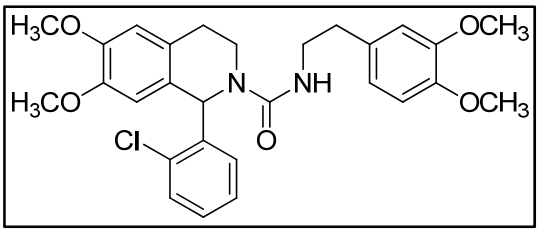
Obtained according to the general procedure **5.2.2** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluene sulfinic acid (0.24 g, 1.53 mmol, 3equiv.), butyraldehyde (0.11 g, 1.53 mmol) and AcOEt (5.0 mL) as solvent. Purification by flash column chromatography on silica gel using 8:2 diethyl ether: ethyl acetate as eluent afforded the product **7f** (0.12 g, 0.27 mmol) as a pale brown solid in 52 % yield; **Mp** 78 – 80 ºC; **IR (NaCl) ν_{max}** 3320, 2960, 1530 cm-^{1}; **Anal.** Calcd for $C_{25}H_{34}N_2$: C, 67.85; H, 7.74; N, 6.33. Found: C, 67.92; H, 7.55; N, 6.44.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.73 (d, *J* = 8.7 Hz, 1H, **H5'''**), 6.69 – 6.59 (m, 2H, **H2''', H6'''**), 6.54 (s, 1H, **H5**), 6.52 (s, 1H, **H8**), 4.87 (dd, *J* = 7.8, 5.9 Hz, 1H, **H1**), 4.57 (t, *J* = 5.2 Hz, 1H, **NH**), 3.80 (s, 3H, OCH_3), 3.80 (s, 6H, 2xOCH_3), 3.76 (s, 3H, OCH_3), 3.73 – 3.59 (m, 1H, **H3**), 3.54 – 3.33 (m, 2H, **H1''**), 3.31 – 3.17 (m, 1H, **H3**), 2.82 – 2.57 (m, 4H, **H4, H2''**), 1.80 – 1.49 (m, 2H, **H1'**), 1.41 – 1.23 (m, 2H, **H2'**), 0.87 (t, *J* = 7.3 Hz, 3H, **H3'**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 157.4 (N**C**ON), 148.8, 147.5, 147.4, 147.1 (4x**OC**H_3), 131.9 (**C1'''**), 130.3 (**C4a**), 126.0 (**C8a**), 120.6 , 111.9 (**C6''',*C2'''**), 111.2 , 111.1 (**C5''', C4a**), 110.1 (**C8**), 55.9, 55.8, 55.7(4x**OC**H_3), 54.5 (**C1**), 42.2 (**C1''**), 39.1 (**C1'**), 38.3 (**C3**), 35.8 (**C2''**), 27.5 (**C4**), 20.0 (**C2'**), 14.0 (**C3'**).

5.2.2.6. Sinthesis of (R*)-1-ethyl-6,7-dimethoxy-*N*'-(4,5-dimethoxy-2-(1-tosylpropyl)phenethyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxamide 7g.



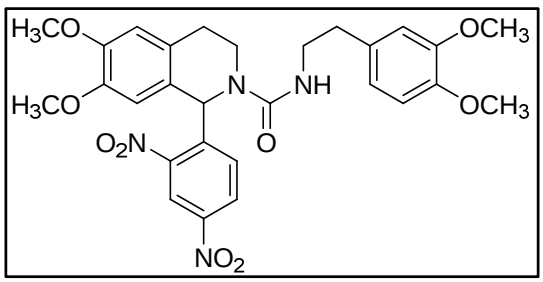
Obtained according to the general procedure **5.2.2** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluenesulfinic acid (0.18 g, 1.12 mmol, 2.2 equiv), propionaldehyde (0.12 g, 2.04 mmol, 4.0 equiv) and DCM (5.0 mL) as solvent. Purification by flash column chromatography on silica gel using 9:1 diethyl ether:ethyl acetate as eluent afforded the product **7g** (0.19 g, 0.30 mmol) as a pale brown solid in 60 % yield; **Mp** 90 – 92ºC; **IR (NaCl) ν_{max}** 3300, 2980, 1535 cm^{-1}; **Anal.** Calcd. for $C_{25}H_{34}N_2$: C, 65.36; H, 7.10; N, 4.48; S, 5.13. Found: C, 65.35; H, 7.16; N, 4.44; S, 5.16; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.57* (d, *J* = 8.2 Hz, 1H, **H3^V**), 7.48* (d, *J* = 8.2 Hz, 1H, **H5^V**), 7.21** (d, *J* = 8.1 Hz, 1H,**H1^V**), 7.15** (d, *J* = 8.1 Hz, 1H**, *H6^V**), 6.80 (s, 0.5H, **H8**), 6.69 (s, 0.5H, **H8**), 6.59 (s, 0.5H, **H5**), 6.56 (s, 0.5H, **H5**), 6.52 (sa, 1H, **H5'''**), 6.51 (s, 1H, **H2'''**), 5.08 – 4.90 (m, 1H, N**H**), 4.89 – 4.71 (m, 1H, **H1^{IV}**), 4.41 (dd, *J* = 11.3, 3.4 Hz, 1H, **H1**), 3.78 – 3.63 (m, 12H, 4xOC**H$_3$**), 3.63 – 3.09 (m, 4H, **H3, H1''**), 2.85 – 2.47 (m, 4H, **H4, H2''**), 2.36 (s, 1.5H, Ar- C**H$_3$**), 2.33 (s, 1.5H, Ar-C**H$_3$**), 2.30 – 2.14 (m, 1H, **H1'**), 2.06 - 1.88 (m, 1H, **H1'**), 1.84 – 1.64 (m, 2H, **H2^{IV}**), 0.87 (dd, *J* = 12.5, 7.5 Hz, 3H, **H3^{IV}**), 0.73 (dd, *J* = 12.5, 7.5 Hz, 3H, **H2'**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 157.8, 157.8 (NCON), 149.0, 148.9 (**C6**), 147.6, 147.6, 147.5 (**C3''', C4'''**), 147.2 (**C7**), 144.8, 144.8 (**C1^V**), 134.9, 134.6 (**C4^V**), 133.2, 133.1 (**C8a**), 130.3, 130.2 (**C6^V**), 129.7, 129.5 (**C2^V, C6^V**), 129.4, 129.3 (**C3^V, C5^V**), 126.2, 126.2 (**C1'''**), 121.7 (**C4a**), 113.2, 112.8 (**C5**), 111.3, 111.3 (**C2'''**), 110.8, 110.7 (**C8**), 110.3, 110.3 (**C5'''**), 67.1, 67.0 (**C1**), 56.0, 56.0, 55.8, 55.7 (4xOCH_3), 55.7 (**C1^V**), 41.5, 41.4, 38.4, 38.3 (**C3, C1''**), 32.7, 32.4 (**C4**), 29.8, 29.8, 29.7 (**C2^{IV}**), 27.7, 27.59 (**C2''**), 23.2, 22.8 (**C2'**), 21.8, 21.7 (Ar - CH_3), 11.4, 11.3, 11.2 (**C2', C3^V**).

5.2.2.7. Sinthesis of 1-(2-chlorophenyl)-6,7-dimethoxy-*N*'-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxamide 7h.



Obtained according to the general procedure **5.2.2** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluenesulfinic acid (0.24 g, 1.53 mmol, 3 equiv), 2-chlorobenzaldehyde (0.22 g, 1.57 mmol) and AcOEt (5.0 mL) as solvent. Purification by flash column chromatography on silica gel using 8:2 diethyl ether:ethyl acetate as eluent afforded the product **7h** (0.14 g, 0.27 mmol) as a pale yellow solid in 54 % yield; **Mp** 72 – 74ºC; **IR (NaCl) ν_{max}** 3300, 2980, 1535 cm^{-1}; **Anal.** Calcd. for $C_{28}H_{31}N_2$: C, 65.81; H, 6.11; N, 5.48 Found: C, 65.75; H, 6.16; N, 5.44; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 7.3, 2.0 Hz, 1H, **H3'**), 7.20 – 7.06 (m, 2H, **H4', H5'**), 6.99 (dd, *J* = 7.5, 2.0 Hz, 1H, **H6'**), 6.76 – 6.67* (m, 1H, **H5'''**), 6.66 – 6.58* (m, 3H, **H2''', H6''', H5**), 6.42 (s, 1H, **H8**), 6.22 (s, 1H, **H1**), 4.86 (t, *J* = 5.5 Hz, 1H, **NH**), 3.98 (ddd, *J* = 13.2, 5.0, 3.1 Hz, 1H, **H3**), 3.83 (s, 3H, OC**H$_3$**), 3.82 (s, 3H, OC**H$_3$**), 3.76 (s, 3H, OC**H$_3$**), 3.67 (s, 3H, OC**H$_3$**), 3.52 – 3.39 (m, 2H, **H1'**), 3.30 (ddd, *J* = 13.7, 10.9, 4.1 Hz, 1H, **H3**), 2.92 (ddd, *J* = 16.1, 10.8, 5.4 Hz, 1H, **H4**), 2.75 – 2.62 (m, 3H, **H4, H2''**);); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 157.7 (CO), 148.8, 148.0, 147.6, 147.4 (4xC-OCH_3), 140.7 (**C1'**), 133.0 (**C2'**), 131.7 (**C1'''**), 130.4 (**C6'**), 129.7 (**C3'**), 128.9* (**C4'**), 127.2** (**C4a), 127.1*** (**C5'**), 126.8** (**C8a**), 120.5, 111.8, 111.3, 111.2 (**C5, C2''', C5''', C6'''**), 110.3 (**C8**) , 55.9, 55.8, 55.7 (4xO**C**H_3), 55.2 (**C1**), 42.1 (**C1''**), 38.9 (**C3**), 35.6 (**C2''**), 27.6 (**C4**).

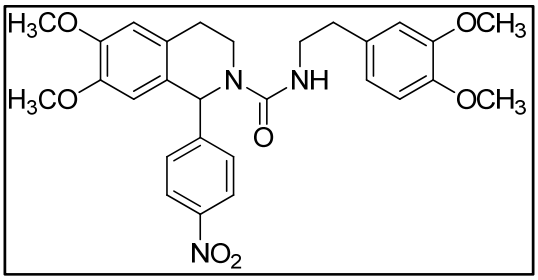
5.2.2.8. Synthesis of 6,7-dimethoxy-*N*'-(3,4-dimethoxyphenethyl)-1-(2,4-dinitrophenyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxamide 7i.



Obtained according to the general procedure **5.2.2** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluenesulfinic acid (0.24 g, 1.53 mmol, 3 equiv), 2,4-dinitrobenzaldehyde (0.30 g, 1.53 mmol) and AcOEt (5.0 mL) as solvent. Purification by flash column chromatography on silica gel using 8:2 diethyl ether:ethyl acetate as eluent afforded the product **7i** (0.15 g, 0.26 mmol) as a pale

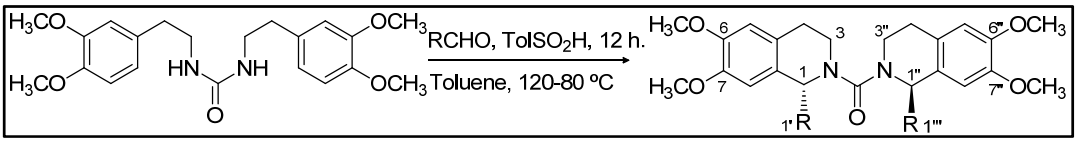
brown solid in 50 % yield as a mixture of rotamers in $CDCl_3$, 25 ºC; **Mp** 143 – 146 ºC; **IR (NaCl) ν_{max}** 3150, 1972, 1519, 1320 cm^{-1}; **Anal.** Calcd. for $C_{28}H_{30}N_4$: C, 59.36; H, 5.34; N, 9.89 Found: C, 59.34; H, 5.40; N, 10.00; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.54* (s, 1H, **H3'**), 7.73* (dd, *J* = 4.3, 1.2 Hz, 1H, **H2'''**), 7.15 – 7.10** (m, 1H, **H5'**), 7.00 (d, *J* = 8.0 Hz, 1H, **H5''**), 6.94* (d, *J* = 1.8 Hz, 1H, **H6'''**), 6.90 – 6.86** (m, 1H, **H6'**), 6.63 (s, 1H, **H8**), 6.56 (s, 1H, **H5**), 6.33 (s, 1H, **H1**), 5.04 – 4.71 (m, 1H, **NH**), 3.95 – 3.77 (m, 12H, OCH_3), 3.57 – 3.30 (m, 4H, **H3, H1'**), 2.99 – 2.59 (m, 4H, **H4, H2''**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 168.9 (NCON), 157.3, 156.1 (**C2', C4'**), 151.7, 150.1, 148.2, 148.0, 147.6 (4x**C**-OCH_3), 138.7, 138.7 (**C1'**), 133.0 (**C1'''**), 129.7, 129.5 (**C5'**), 127.9 (**C4a**), 127.0 (**C8a**), 123.3* (**C2''**), 118.0 (**C1''**), 117.8* (**C6''**), 116.6 (**C1''**), 115.3* (**C3'**), 115,0 (**C6'**), 114.2* (**C5''**), 113.4* (**C2''**), 112.5* (**C3'**), 111.3, 111.1 (**C5, C8**), 56.4 (**C1**), 56.2, 56.1, 56.1 (4xOCH_3), 42.5 (**C1''**), 39.3 (**C3**), 34.1 (**C2''**), 27.7 (**C4**).

5.2.2.9. Synthesis of 6,7-dimethoxy-*N*'-(3,4-dimethoxyphenethyl)-1-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxamide 7j.



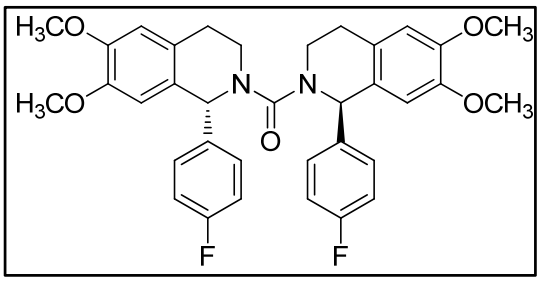
Obtained according to the general procedure **5.2.2** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluenesulfinic acid (0.24 g, 1.53 mmol, 3 equiv), 4-nitrobenzaldehyde (0.23 g, 1.52 mmol) and AcOEt (5.0 mL) as solvent. Purification by flash column chromatography on silica gel using 8:2 diethyl ether:ethyl acetate as eluent afforded the product **7j** (0.066 g, 0.13 mmol) as a pale brown solid in 25 % yield, as a mixture of rotamers in $CDCl_3$, 25 ºC; **Mp** 163 – 166ºC; **IR (NaCl) ν_{max}** 3150, 1972, 1519, 1320 cm^{-1}; **Anal.** Calcd. for $C_{28}H_{31}N_3$: C, 64.48; H, 5.99; N, 8.06. Found: C, 64.34; H, 5.90; N, 8.00; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.19 – 8.06* (m, 4H, **H2', H6', H2''', H6'''**), 7.45 – 7.33* (m, 3H, **H3', H5', H5'''**), 6.71** (s, 1H, **H5**), 6.69** (s, 1H, **H8**), 6.54 (s, 0.33H, **H1**), 6.51 (s, 0.68H, **H1**), 4.10 – 4.00 (m, 1H, N**H**), 3.92 – 3.75 (m, 12H, 4xOCH_3), 3.65 – 3.26 (m, 4H, **H3, H1''**), 3.09 – 2.60 (m, 4H, **H4, H2''**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 157.4 (NCON), 150.5, 149.2, 148.7, 147.9, 147.8, 147.1 (**C1'**, 4x**C**-OCH_3), 131.7 (**C1''**), 129.6, 129.2, 128.7 (**C3', C4'**), 127.1, 127.0 (**C4a, C8a**), 124.4 , 124.0, 123.6 (**C2', C6**'), 120.8, 112.1, 111.4, 111.4, 111.1, 111.1 (**C5, C8, C2''', C5''', C6'''**), 56.4, 56.2, 56.1, 56.0, 55.9 (**C1**, 4xOCH_3), 42.3 (**C1''**), 40.2 (**C3**), 35.8 (**C2''**), 27.6 (**C4**).

5.2.3. General procedure to obtain (±) (*R*)-Bis -6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone 7ka – 7ki.



To a solution of compound **3** (1.0 equiv.) in toluene (5.0 mL) was added aryl or alkyl aldehyde (3 equiv.), *p*-toluene sulfinic acid (1.1 – 3.0 equiv.) to 120 - 80 ºC for 12 h. The mixture was quenched with a saturate solution of Na_2HCO_3, was extracted with DCM (2x30 mL) and concentrated under reduced pressure. The crude was purified by flash column chromatography using a mixture petroleum ether: diethyl ether to give the compounds **7ka – 7ki**.

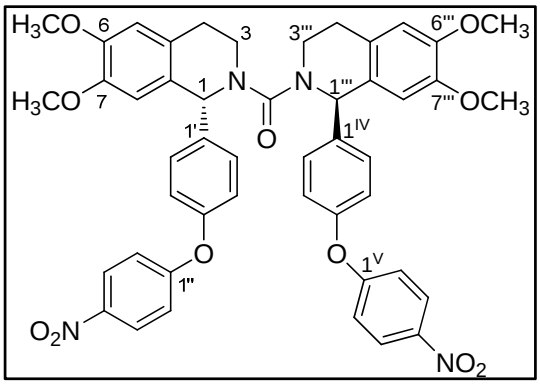
5.2.3.1. Synthesis of (±) (*R*)-Bis -1-(4-fluorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone 7ka.



Obtained according to the general procedure **5.2.3** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluene sulfinic acid (0.24 g, 1.53 mmol, 3equiv.), 4-fluorobenzaldehyde (0.19 g, 1.52 mmol) and toluene (5.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether: diethyl ether as eluent afforded the product **7ka** (0.081 g, 0.13 mmol) as a pale yellow solid in 30 % yield as a mixture of rotamers in $CDCl_3$, 25 ºC; **Mp** 105 - 107 ºC; **IR(NaCl)** ν_{max} 3076, 1930, 1220 cm^{-1}; **Anal**. Calcd for $C_{35}H_{34}N_2$: C, 69.99; H, 5.71; N, 4.66. Found: C, 69.65; H, 5.67; N, 4.50; **LRMS** (ES): m/z: (rel. intensity %) 623 ($[M+Na]^+$, 100) ; **HRMS** (ES^+): Calcul. for $C_{35}F_2H_{34}N_2NaO_5^+$ $[M+Na]^+$ m/z: 623.2333, found m/z: 623.2331 **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.16 – 7.03 (m, 4H, **H2', H6', H2''', H6'''**), 6.98 – 6.89 (m, 4H, **H3', H5', H3''', H5'''**), 6.65* (s, 1H, **H8''**), 6.64* (s, 1H, **H8**), 6.41** (s, 1H, **H5**), 6.39** (s, 1H, **H5''**), 6.08† (s, 1H, **H1**), 5.98† (s, 1H, **H1'**), 3.87 (s, 6H, 2xOCH_3), 3.71 (s, 1H, 3H, OCH_3), 3.74 (s, 3H, 3H, OCH_3), 3.67 – 3.53†† (m, 2H, **H3**), 3.33 – 2.99†† (m, 2H, **H3''**), 2.91 – 2.60 (m, 4H, **H4, H4''**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 162.5* (d, *J*= 270.0 *Hz*, **H4'**), 161.8* (d, *J*= 270.0 *Hz*, **H4'''**), 163.3, 164.0

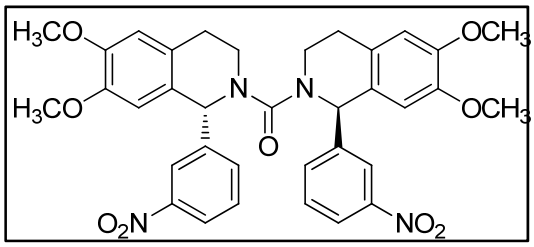
(N**C**ON), 148.2, 148.1 (**C6, C6''**), 147.7, 147.5 (**C7, C7''**), 139.1, 139.0, 138.4, 138.3 (**C1', C1'''**), 130.8, 130.6, 130.5, 130.4 (**C2', C2''', C6',C6'''**), 127.8, 127.1 (**C4a, C4a''**), 126.6, 126.4 (**C8a, C8a''**), 115.3, 115.1, 114.9, 114.7 (**C3', *C3''', C5', C5'''**), 111.3, 111.2 (**C8, C8''**), 111.1, 111.0 (**C5, C5''**), 58.6, 58.2 (**C1, C1''**), 56.0, 55.9 (4xO**C**H_3), 41.2, 41.1 (**C3, C3''**), 28.7, 28.0 (**C4, C4''**).

5.2.3.2. Synthesis of (±) (*R*)-Bis-6,7-dimethoxy-1-(4-(4-nitrophenoxy)phenyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone 7kb.



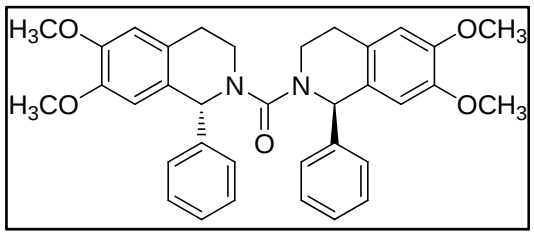
Obtained according to the general procedure **5.2.3** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluene sulfinic acid (0.24 g, 1.53 mmol, 3equiv.), 4-(4-nitrophenoxy)benzaldehyde (0.37 g, 1.52 mmol) and toluene (5.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using diethyl ether as eluent afforded the product **7kb** (0.09 g, 0.11 mmol) as a pale yellow solid in 21 % yield; **Mp** 114 - 116 ºC; **IR (NaCl) ν_{max}** 3050, 1940, 1580, 1340 cm^{-1} **Anal.** Calcd for $C_{47}H_{42}N_4$: C, 67.29; H, 5.05; N, 6.68 Found: C, 67.10; H, 5.06; N, 6.69.**^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.5 Hz, 4H, **H3'', H5'', H3^V, H5^V**), 7.26 (d, *J* = 7.5 Hz, 4H, **H2', H6', H2^{IV}, H6^{IV}**), 6.94 (d, *J* = 7.5 Hz, 4H, **H3', H5', H3^{IV}, H5^{IV}**), 6.94 (d, *J* = 7.5 Hz, 4H, **H2'', H6'', H2^V, H6^V**), 6.64 (s, 2H, **H5**, **H5'''**), 6.59 (s, 2H , **H8, H8'''**) 6.40 (s, 2H, **H1**, **H1'''**), 3.83 (s, 6H, 2xOC**H$_3$**), 3.75 (s, 6H, 2xOC**H$_3$**), 3.64 – 3.53* (m, 2H, **H3**), 3.44 – 3.34* (m, 2H, **H3'''**), 2.93 – 2.81** (m, 2H, **H4**), 2.67** (dt, *J* = 15.8, 4.9 Hz, 2H, **H4'''**).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.1 (**C1'', C1^V**), 158.3 (NCON), 153.7 (**C4', C4^{IV}**), 148.2, 147.5 (4x**C**-OCH$_3$), 142.5 (**C4'', C4^V**), 139.8 (**C1', C1^{IV}**), 129.8 (**C2', C6', C2^{IV}, C6^{IV}**), 127.4 (**C4a, C4a ^{IV}**), 126.9 (**C8a, C8a ^{IV}**), 125.8 (**C3'', C3^V**), 120.1 (**C2'', C6'', C2^V, C6^V**), 117.0 (**C2', C6', C2^{IV}, C6^{IV}**), 111.2 (**C8, C8'''**), 111.0 (**C5**, **C5'''**), 56.0 (**C1, C1'''**), 55.9, 55.8 (4xOCH$_3$), 39.8 (**C3, C3'''**), 27.7 (**C4, C4'''**).

5.2.3.3. Synthesis of (±) (*R*)-Bis(6,7-dimethoxy-1-(3-nitrophenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone 7kc.



Obtained according to the general procedure **5.2.3** using the compound **3** (0.20 g, 0.51 mmol) as starting, material *p*-toluene sulfinic acid (0.24 g, 1.53 mmol, 3equiv.), 3-nitrobenzaldehyde (0.23 g, 1.52 mmol) and Toluene (5 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether: diethyl ether as eluent afforded the product **7kc** (0.28 g, 0.42 mmol) as a pale yellow solid in 82 % yield; **Mp** 94 - 96 ºC; **IR (NaCl)** ν_{max} 3080, 1960, 1584, 1339 cm^{-1}. **Anal.** Calcd for $C_{35}H_{34}N_4$: C, 64.21; H, 5.23; N, 8.56. Found: C, 64.10; H, 5.06; N, 8.52; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.15 – 8.04 (m, 2H, **H4', H4'''**), 8.04 – 7.98 (m, 2H, **H2', H2'''**), 7.61 – 7.51 (m, 2H, **H6', H6'''**), 7.50 – 7.32 (m, 2H, **H5', H5'''**), 6.68* (s, 1H, **H5**), 6.67* (s, 1H, **H5''**), 6.40** (s, 1H, **H8**), 6.36** (s, 1H, **H8''**), 6.18† (s, 1H, **H1**), 6.07† (s, 1H, **H1''**), 3.88 (s, 6H, 2xOC**H$_3$**), 3.74 – 3.57†† (m, 8H, 2xOC**H$_3$, H3**), 3.21†† (m, 2H, **H3''**), 3.12 – 2.73 (m, 4H, **H4, H4''**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 163.5, 163.3 (NCON), 148.5, 148.4 (**C6, C6''**), 148.2 (**C1', C1'''**), 147.9, 147.8 (**C7, C7''**), 145.4, 144.7 (**C3', C3'''**), 135.2, 134.9 (**C6', C6'''**), 129.4, 129.1 (**C5', C5'''**), 126.6, 126.4, 126.3, 125.6 (**C4a, C4a'', C8a, C8a''**), 123.6, 123.2 (**C2', C2'''**), 122.6, 122.5 (**C4', C4'''**), 111.5 (**C5, C5''**), 110.8 (**C8, C8''**), 58.7, 58.4 (**C1, C1''**), 56.0, 55.9 (4xOCH_3), 41.9, 41.8 (**C3, C3''**), 28.5, 28.0 (**C4, C4''**).

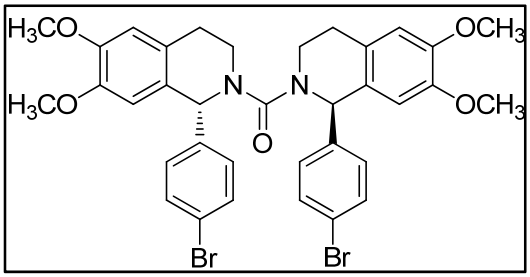
5.2.3.4. Synthesis of (±) (*R*)-Bis-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone 7kd.



Obtained according to the general procedure **5.2.3** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluene sulfinic acid (0.24 g, 1.53 mmol, 3equiv.), benzaldehyde (0.16 g, 1.52 mmol) and toluene (5.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether: diethyl ether as eluent afforded the product **7kc** (0.21 g, 0.37 mmol) as a pale yellow solid in 73 % yield as a mixture of rotamers in $CDCl_3$, 25 ºC; **Mp** 104 - 106 ºC; **IR (NaCl)** ν_{max} 3060, 1960 cm^{-1}; **Anal**. Calcd for $C_{35}H_{36}N_2$: C, 74.45; H, 6.43; N, 4.96. Found: C, 74.25; H, 6.51; N, 5.00; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.33 – 7.08 (m, 10H, **H2' - H6',**

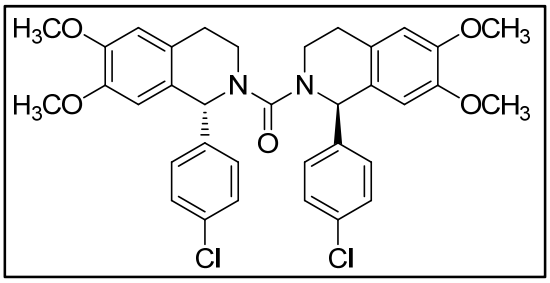
H2''' - H6'''), 6.68* (s, 1H, **H5**), 6.67* (s, 1H, **H5''**), 6.50** (s, 1H, **H8**), 6.47** (s, 1H, **H8''**), 6.14† (s, 2H, **H1**), 6.09† (s, 2H, **H1''**), 3.90 (s, 6H, 2xOC**H$_3$**), 3.79 – 3.71 (m, 6H, 2xOC**H$_3$**), 3.70 – 3.57†† (m, 2H, **H3**), 3.41 – 3.13†† (m, 2H, **H3''**), 3.11 – 2.79# (m, 2H, **H4**), 2.79 – 2.61# (m, 2H, **H4''**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 163.8, 163.4 (N**C**ON), 148.0, 147.9, 147.4, 147.3 **(C6, C6'', C7, C7'')**, 143.1, 142.5 (**C1', C1'''**), 128.9, 128.8, 128.2, 128.1*(**C3', C2', C5', C6'**), 127.9** (**C4a**), 127.3* (**C4', C4'''**), 127.2** (**C8a**), 127.1* (**C2''', C3''', C5''', C6'''**), 126.7, 126.5** (**C4a'', C8a''**), 111.3, 111.2 (**C5, C5''**), 111.1, 111.0 (**C8, C8''**), 59.3, 58.9 (**C1, C1''**), 55.9, 55.9 (4xO**C**H$_3$), 41.0, 40.9 (**C3, C3''**), 28.6, 27.8 (**C4, C4''**).

5.2.3.5. Synthesis of (±) (*R*)-Bis-1-(4-bromophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone 7ke.



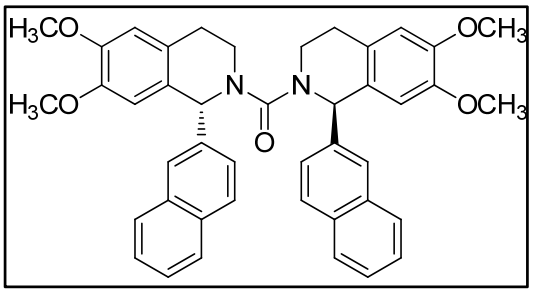
Obtained according to the general procedure **5.2.3** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluene sulfinic acid (0.24 g, 1.53 mmol, 3equiv.), 4-bromobenzaldehyde (0.28 g, 1.52 mmol) and toluene (5.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether: diethyl ether as eluent afforded the product **7ke** (0.15 g, 0.21 mmol) as a pale orange solid in 41 % yield as a mixture of rotamers in $CDCl_3$, 25ºC; **Mp** 90 - 92 ºC; **IR (NaCl) ν_{max}** 3065, 1964 cm^{-1}; **Anal**. Calcd for $C_{35}H_{34}N_2$: C, 58.19; H, 4.74; N, 3.88. Found: C, 58.40; H, 4.90; N, 4.00.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 4H, **H3', H5', H3''', H5'''**), 7.05 – 6.90 (m, 4H, **H2', H6', H2''', H6'''**), 6.65* (s, 1H, **H5**), 6.63* (s, 1H, **H5''**), 6.41** (s, 1H, **H8**), 6.38** (s, 1H, **H8''**), 6.05† (s, 1H, **H1**), 5.94† (s, 1H, **H1''**), 3.87 – 3.71 (m, 12H, 4xOC**H$_3$**), 3.67 – 3.53†† (m, 2H, **H3**), 3.15†† (m, 2H, **H3''**), 2.77 (s, 4H, **H4, H4''**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 163.6, 163.3 (N**C**ON), 148.2, 148.1, 147.7, 147.6 (**C6, C7, C6'', C7''**), 142.3, 141.6 (**C1', C1'''**), 131.4, 131.2 (**C3', C5', C3''', C5'''**), 130.8, 130.5 (**C3', C5', C3''', C5'''**), 127.3, 126.7, 126.6, 126.4 (**C4a, C8a, C4a'', C8a''**), 121.5, 121.4 (**C4', C4'''**), 111.3, 111.2 (**C5, C5''**), 110.9 (**C8, C8''**), 58.7, 58.2 (**C1, C1''**), 56.0, 55.9, 55.9 (4x OCH_3), 41.4, 41.3 (**C3, C3''**), 28.6, 28.5 (**C4, C4''**).

5.2.3.6. Synthesis of (±) (*R*)-Bis-1-(4-chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone 7kf.



Obtained according to the general procedure **5.2.3** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluene sulfinic acid (0.24 g, 1.53 mmol, 3equiv.), 4-chlorobenzaldehyde (0.21 g, 1.52 mmol) and toluene (5.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using diethyl ether as eluent afforded the product **7kf** (0.12 g, 0.19 mmol) as a pale orange solid in 37 % yield as a mixture of rotamers in $CDCl_3$, 25ºC; **Mp** 103 - 105 ºC; **IR (NaCl)** ν_{max} 3065, 1964 cm^{-1}; **Anal**. Calcd for $C_{35}H_{34}N_2$: C, 66.35; H, 5.41; N, 4.42 Found: C, 66.40; H, 5.30; N, 4.25.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.33 7.17* (m, 4H, **H2', H6', H2''', H6'''**), 7.17 – 7.04* (m, 4H, **H3', H5', H3''', H5'''**), 6.70** (s, 1H, **H5**), 6.69** (s, 1H, **H5''**), 6.47† (s, 1H, **H8**), 6.43† (s, 1H, **H8''**), 6.12†† (s, 1H, ***H1**), 6.02†† (s, 1H, **H1''**), 3.93 (s, 6H, 2xOC**H$_3$**), 3.80, 3.76 (s, 6H, 2xOC**H$_3$**), 3.71 – 3.55$^{\#}$ (m, 2H, **H3**), 3.43 – 2.96$^{\#}$ (m, 2H, **H3''**), 2.96 – 2.62 (m, 4H, **H4, H4''**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 163.6, 163.3 (N**C**ON), 148.2, 148.1 (**C6, C6''**), 147.6, 147.5 (**C7, C7''**), 141.8, 141.0 (**C1', C1'''**), 133.3, 133.2 (**C4', C4'''**), 130.4, 130.1 (**C2', C6', C2''', C6'''**), 128.5, 128.3 (**C3', C5', C3''', C5'''**), 127.4, 126.8, 126.6, 126.4 (**C4a, C4a'', C8a, C8a''**), 111.3, 111.2 (**C5, *C5''**), 110.9 (**C8, C8''**), 58.7, 58.2 (**C1, C1''**), 56.0, 55.9 (4xO**C**H$_3$), 41.3, 41.2 (**C3, *C3''**), 28.6, 27.9 (**C4, C4''**).

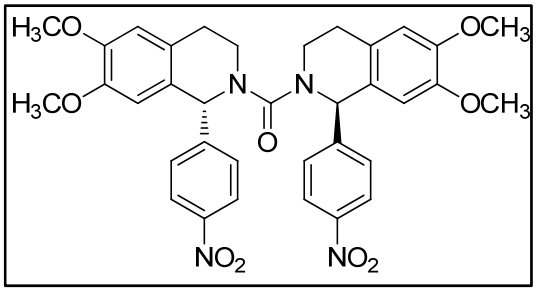
5.2.3.7. Synthesis of (±) (*R*)-Bis-6,7-dimethoxy-1-(naphthalen-2-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone 7kg.



Obtained according to the general procedure **5.2.3** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluene sulfinic acid (0.24 g, 1.53 mmol, 3equiv.), 2-naphaldehyde (0.24 g, 1.52 mmol) and toluene (5.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using diethyl ether as eluent afforded the product **7kg** (0.13 g, 0.20 mmol) as a pale yellow solid in 40 %

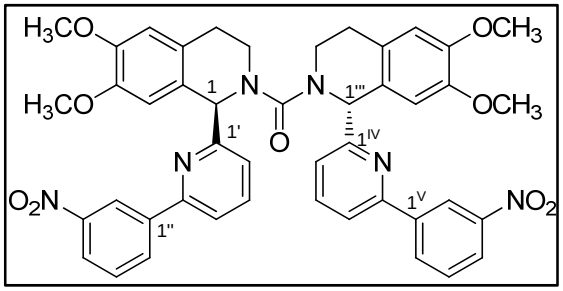
yield as a mixture of rotamers in $CDCl_3$, 25ºC; **Mp** 118 – 120 ºC; **IR (NaCl) ν_{max}** 3060, 1961 cm^{-1}; **Anal**. Calcd for $C_{43}H_{40}N_2$: C, 77.69; H, 6.06; N, 4.21 Found: C, 77. 50; H, 6.10; N, 4.25.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.63 – 7.37 (m, 6H, **$CH_{Ar\text{-}naphthyl}$**), 7.30 – 7.04 (m, 8H, **$CH_{Ar\text{-}naphthyl}$**), 6.51 (s, 1H, **H5, H5''**), 6.50 (s, 1H, **H5, H5''**), 6.33 (s, 2H, **H8, H8''**), 6.15 (s, 1H, **H1, H1''**), 6.02 (s, 1H, **H1, H1''**), 3.71 (s, 6H, 2x**OCH_3**), 3.53 (s, 2H, **OCH_3**), 3,50 (s, 4H, **OCH_3**), 3.60 – 3.40 (m, 2H, **H3, H3''**), 3.25 – 2.99 (m, 2H, **H3, H3''**), 2.99 – 2.40 (m, 4H, **H4, H4''**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 163.9, 163.4 (N**C**ON), 148.0, 147.5, 147.3 (**C6, C6'', C7, C7''**), 140.7, 140.0 (**C1', C1'''**), 133.0, 132.9, 132.7, 132.6 (**C4a', C4a''', C8a', C8a'''**), 128.1, 127.9, 127.8 (**$CH_{Ar\text{-}naphthyl}$**), 127.7* (**C4a**), 127.7, 127.5, 127.5, 127.1, 126.8 (**$CH_{Ar\text{-}naphthyl}$**), 126.8* (**C4a''**), 126.7, 126.6* (**C8a, C8a''**), 126.1, 126.0, 125.9 (**$CH_{Ar\text{-}naphthyl}$**), 111.3, 111.2 (**C5, C5''**), 111.1 (**C8, C8''**), 59.5, 58.8 (**C1, C1''**), 55.9 (4x**OCH_3**), 41.3, 41.1 (**C3, C3''**), 28.7, 27.9 (**C4, C4''**).

5.2.3.8. Synthesis of (±) (*R*)-Bis-6,7-dimethoxy-1-(4-nitrophenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone 7kh.



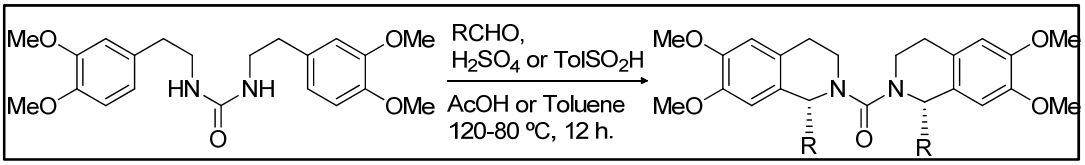
Obtained according to the general procedure **5.2.3** using the compound **3** (0.20 g, 0.51 mmol), *p*-toluene sulfinic acid (0.24 g, 1.53 mmol, 3equiv.), 2-naphaldehyde (0.24 g, 1.52 mmol) as starting material and toluene (5 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using diethyl ether as eluent afforded the product **7kg** (0.13 g, 0.20 mmol) as a pale yellow solid in 40 % yield as a mixture of rotamers in $CDCl_3$, 25ºC; **Mp** 130 – 132 ºC; **IR (NaCl) ν_{max}** 3076, 1930, 1347, 1519 cm^{-1}; **Anal**. Calcd for $C_{35}H_{34}N_4$: C, 64.21; H, 5.23; N, 8.56 Found: C, 64.20; H, 5.10; N, 8.46.; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09* (d, *J* = 8.7 Hz, 2H, **H3', H5'**), 8.01* (d, *J* = 8.8 Hz, 2H,**H3''', H5'''**), 7.35** (d, *J* = 8.4 Hz, 2H, **H2', H6'**), 7.33** (d, *J* = 8.7 Hz, 2H, **H2''', H6'''**), 6.67† (s, 1H, **H5**), 6.64† (s, 1H, **H5''**), 6.41$^{\dagger\,\dagger}$ (s, 1H, **H8**), 6.34$^{\dagger\,\dagger}$ (s, 1H, **H8''**), 6.17$^{\#}$ (s, 1H, **H1**), 6.06$^{\#}$ (s, 1H, **H1''**), 3.85 (s, 6H, 2x**OCH_3**), 3.72 (s, 2H, **OCH_3**), 3.67 (s, 4H, 2x**OCH_3**), 3.65 – 3.49$^{\#\#}$ (m, 2H, **H3**), 3.37 – 3.13$^{\#\#}$ (m, 2H, **H3''**), 3.10 – 2.70 (m, 4H, **H4, H4''**).; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.3, 163.2 (N**C**ON), 150.6, 149.7 (**C1', C1'''**), 148.5, 148.4, 147.8, 147.7 (**C6, C6'', C7, C7''**), 147.1, 147.0 (**C4', C4'''**), 129.8, 129.4 (**C2', C6', C2''', C6'''**), 126.3, 126.2 (**C4a, C4a''**), 125.7 (**C8a, C8a''**), 123.5, 123.2 (**C3', C5', C3''', C5'''**), 111.4, 111.3 (**C5, C5''**), 110.7 , 110.7 (**C8, C8''**), 58.6, 58.0 (**C1, C1''**), 55.9, 55.9, 55.8 (4x**OCH_3**), 42.1, 41.7 (**C3, C3''**), 28.6, 27.8 (**C4, C4''**).

5.2.3.9. Synthesis of (±) (*R*)-Bis-6,7-dimethoxy-1-(6-(3-nitrophenyl)pyridin-2-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone 7ki.



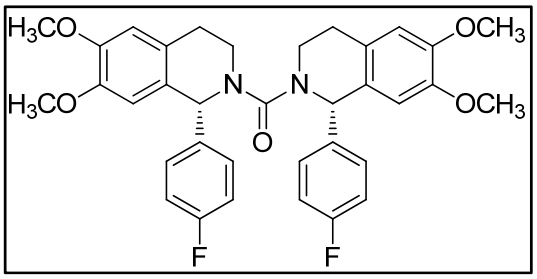
Obtained according to the general procedure **5.2.3** using the compound **3** (0.20 g, 0.51 mmol) as starting material, sulfuric acid 98 % (0.092 g, 0.94 mmol, 1.8 equiv.), 6-(3-nitrophenyl)picolinaldehyde (0.35 g, 1.52 mmol) and AcOH (2.0 mL) as solvent at 80 ºC. Purification by flash column chromatography on silica gel using diethyl ether as eluent afforded the product **7ki** (0.27 g, 0.34 mmol) as a pale orange solid in 66 % yield as a mixture of rotamers in $CDCl_3$, 25ºC; **Mp** 139 – 140 ºC; **IR (NaCl)** ν_{max} 3070, 1940, 1347, 1519 cm^{-1}; **Anal.** Calcd for $C_{45}H_{40}N_6$: C, 66.82; H, 4.98; N, 10.39. Found: C, 66.70; H, 4.86; N, 10.19; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.81* (t, 1.8 Hz, 1H, **H6'**), 8.77* (t, 1.8 Hz, 1H, **H6^{IV}**), 8.28 – 8.13** (m, 4H, **H5', H5^{IV}, H2'', H4''**), 7.74 – 7.57** (m, 4H, **H5'', H2^{V}, H4^{V}, H5^{V}**), 7.54 – 7.44 (m, 2H, **H4', H4^{IV}**), 7.27 – 7.10 (m, 2H**, H6'', H6^{V}**), 6.77† (s, 1H, **H8'''**), 6.70† (m, 3H, **H5, H8**, **H5'''**), 6.25†† (s, 1H, **H1**), 6.21†† (s, 1H, **H1'''**), 4.11$^{\#}$ (dd, *J* = 13.0, 4.9 Hz, 2H, **H3**), 3.85 (s, 2H, 2xOC**H$_3$**), 3.85 (s, 4H, 2xOC**H$_3$**), 3.85 (s, 4H, 2xOC**H$_3$**), 3.85 (s, 2H, 2xOC**H$_3$**), 3.67 – 3.50$^{\#}$ (m, 2H, **H3'''**), 3.31 – 3.11$^{\#\#}$ (m, 2H, **H4**), 2.83$^{\#\#}$ (m, 2H, **H4'''**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.2, 164.0 (N**C**ON), 162.2, 162.2 (**C1', C1''**), 153.8, 153.7 (**C3', C3''**), 148.7, 148.6 (**C3'', C3^{V}**), 148.2, 148.1, 147.2, 147.1 (4x**C**-OCH_3), 140.8, 140.7 (**C1'', C1^{V}**), 137.6, 137.5, 137.4, 132.5, 132.4* (**C2'', C4'', C5'', C2^{V}, C4^{V}**), 129.5 (**C4', C4^{IV}**), 127.2, 127.1, 126.5, 126.4 (**C4a, C8a, C4a''', C8a'''**), 123.5, 123.4 (**C5', C5^{IV}**), 122.0, 121.8, 121.6* (**C6', C6^{IV}, C5^{V}**), 118.6 (**C2'', C2^{V}**), 111.4, 111.2, 111.0 (**C5, C8, C5''', C8'''**), 61.9, 61.6 (**C1, C1'''**), 55.9, 55.8, 55.8 (4xO**C**H$_3$), 41.5, 41.4 (**C3, C3'''**), 28.0, 27.9 (**C4, C4'''**).

5.2.4. General procedure to obtain (±) (*S*,R**)-Bis(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone 7ma-7mf.



To a solution of compound **3** (1.0 equiv.) in AcOH or toluene (5.0 mL) the corresponding aryl or alkyl aldehyde (3.0 equiv.) and sulfuric acid or *p*-toluenesulfinic acid (1.8 – 3.0 equiv.) were added at 120 - 80 ºC for 12 h. The mixture was quenched with a saturate solution of $NaHCO_3$, extracted with DCM (2x30 mL) and concentrated under reduced pressure. The crude was purified by flash column chromatography using a mixture of ethyl acetate:methanol to give the compounds **7ma – 7mf**

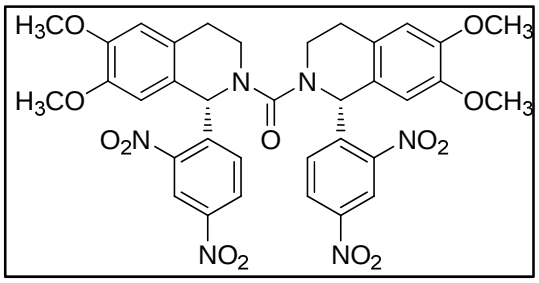
5.2.4.1. (±)-(*R*,S**)-Bis(1-(4-fluorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone 7ma.



Obtained according to the general procedure **5.2.4** using the compound **3** (0.20 g, 0.51 mmol) as starting material sulfuric acid 98 % (0.092 g, 0.94 mmol, 1.8 equiv.), 4-fluorobezanzaldehyde (0.19 g, 1.52 mmol) and AcOH (2.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using 9:1 ethyl acetate: methanol as eluent afforded the product **7ma** (0.12 g, 0.20 mmol) as a pale orange solid in 37 % yield.; **Mp** 177 - 179 ºC; **IR (NaCl) ν_{max}** 3076, 1930, 1228 cm^{-1}; **Anal.** Calcd for $C_{35}H_{34}F_2N_2O_5$: C, 69.99; H, 5.71; N, 4.66. Found: C, 69.80; H, 5.76 ; N, 4.66.; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.24 – 7.15 (m, 4H, **H2', H2''', H6', H6'''**), 6.99 – 6.91 (m, 2H, **H3', H3''', H5', H5'''**), 6.66 (s, 2H, **H8, H8''**), 6.56 (s, 1H, **H5, H5''**), 6.37 (s, 1H, **H1, H1''**), 3.87 (s, 6H, OC**H$_3$**), 3.78 (s, 6H, OC**H$_3$**), 3.59 – 3.53* (m, 2H, **H3**), 3.45 – 3.33* (m, 2H, **H3''**), 2.90** (m, 2H, **H4**), 2.69** (dt, *J* = 15.8, 4.8 Hz, 2H, **H4''**).; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.8, 160.5 (d, *J* = 244.5 Hz, **C4, C4''**) , 158.1 (NCON), 148.3, 147.7 (**C6, C7, C6'', C7''**), 138.5, 138.4 (**C1', C1'''**), 129.8, 129.7 (**C2', C12''',**

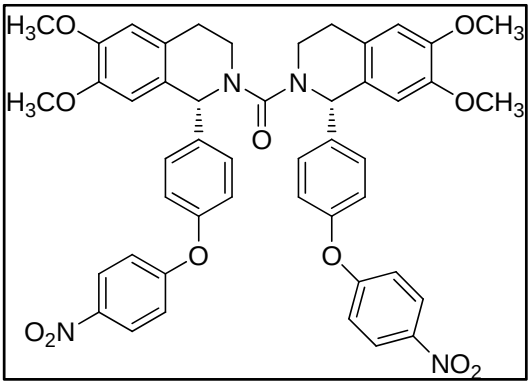
C6', C6'''), 127.5 (**C8a, C8a''**), 126.9 (**C4a, C4a''**), 115.4, 115.1 (**C3', C3''', C5', C5'''**), 111.3 (**C8, C8''**), 111.1 (**C5, C5''**), 56.2 (**C1, C1''**), 56.1, 56.0 (4x OCH_3), 39.9 (**C3, C3''**), 27.9 (**C4, C4''**).

5.2.4.2. Synthesis of (±)-(*R*, S**)-Bis (1-(2,4-dinitrophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone 7mb.



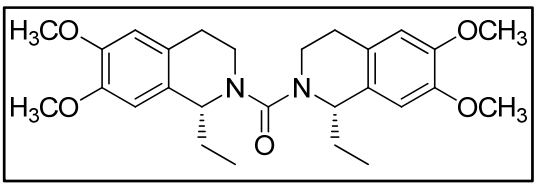
Obtained according to the general procedure **5.2.4** using the compound **3** (0.20 g, 0.51 mmol), sulfuric acid 98 % (0.092 g, 0.94 mmol, 1.8 equiv.), 2,4-dinitrobezanzaldehyde (0.3 g, 1.52 mmol) as starting material and AcOH (2.0 mL) as solvent at 80 ºC. Purification by flash column chromatography on silica gel using 9:1 ethyl acetate:methanol as eluent afforded the product **7mb** (0.083 g, 0.11 mmol) as a brown solid in 22 % yield; **Mp** 128 - 129 ºC; **IR (NaCl) ν_{max}** 3076, 1930, 1567, 1347cm^{-1}; **Anal**. Calcd for $C_{35}H_{32}N_6$: C, 56.45; H, 4.33; N, 11.29 Found: C, 56.20; H, 4.44 ; N, 11.50; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 8.1, 5.6 Hz, 2H, **H5', H5'''**), 6.98 – 6.88 (m, 4H, **H3', H6', H3''',H6'''**), 6.66 (s, 2H, **H8, H8''**), 6.56 (s, 2H, **H5, H5''**), 6.36 (s, 2H, **H1, H1''**), 3.87 (s, 6H, OCH_3), 3.77 (s, 6H, OCH_3), 3.44 – 3.20 (m, 4H, **H3, H3''**), 2.94 – 2.63 (m, 4H, **H4, H4''**); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.7 , 160.5 (**C4', C4'''**), 158.2, 158.1 (NCON), 148.3 (**C7, C7''**), 147.7 (**C6 , C6''**), 138.5, 138.4 (**C2', C2'''**), 129.8, 129.7 (**C5', C5'''**), 127.6 (**C4a, C4a''**), 126.9 (**C8a, C8a''**), 115.4, 115.1 (**C3', C3''', C6', C6'''**), 111.3 (**C8, C8''**), 111.1 (**C5, C5''**), 56.6 (**C1, C1''**), 56.1, 56.0 (4xOCH_3), 39.8 (**C3, C3''**), 27.9 (**C4, C4''**).

5.2.4.3. Synthesis of (±)-(*R**,*S**)-Bis(6,7-dimethoxy-1-(4-(4-nitrophenoxy)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone 7mc.



Obtained according to the general procedure **5.2.4** using the compound **3** (0.20 g, 0.51 mmol) as starting material, sulfuric acid 98 % (0.092 g, 0.94 mmol, 1.8 equiv.), 4-(4-nitrophenoxy)benzaldehyde (0.37 g, 1.52 mmol) and AcOH (2.0 mL) as solvent at 80 ºC. Purification by flash column chromatography on silica gel using ethyl acetate as eluent afforded the product **7mc** (0.16 g, 0.19 mmol) as a pale orange solid in 37 % yield; **Mp** 114 - 116 ºC; **IR (NaCl) ν_{max}** 3050, 1940, 1580, 1340 cm^{-1}; **Anal.** Calcd for $C_{47}H_{42}N_4$: C, 67.29; H, 5.05; N, 6.68. Found: C, 67.10; H, 5.06; N, 6.69; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.5 Hz, 4H, **H3'', H5'', H3^V, H5^V**), 7.26 (d, *J* = 7.5 Hz, 4H, **H2', H6', H2^{IV}, H6^{IV}**), 6.94 (d, *J* = 7.5 Hz, 4H, **H3', H5', H3^{IV}, H5^{IV}**), 6.94 (d, *J* = 7.5 Hz, 4H, **H2'', H6'', H2^V, H6^V**), 6.64 (s, 2H, **H5**, **H5'''**) , 6.59 (s, 2H , **H8, H8'''**) 6.40 (s, 2H, **H1**, **H1'''**), 3.83 (s, 6H, 2xOC**H$_3$**), 3.75 (s, 6H, 2xOC**H$_3$**), 3.64 – 3.53 (m, 2H, **H3**, **H3'''**), 3.44 – 3.34 (m, 2H, **H3**, **H3'''**), 2.93 – 2.81 (m, 2H, **H4**, **H4'''**), 2.67 (dt, *J* = 15.8, 4.9 Hz, 2H, **H4**, **H4'''**); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.1 (**C1'', C1^V**), 158.3 (NCON), 153.7 (**C4', C4^{IV}**), 148.2, 147.5 (4x**C**-OCH$_3$), 142.5 (**C4'', C4^V**), 139.8 (**C1'**, **C1^{IV}**), 129.8* (**C2', C6'**), 127.4 (**C4a, C4a ^{IV}**), 126.9 (**C8a, C8a ^{IV}**), 125.8 (**C3'', C3^V**), 120.1 (**C2'', C6'', C2^V, C6^V**), 117.0* (**C2^{IV}, C6^{IV}**), 111.2 (**C8, C8'''**), 111.0 (**C5**, **C5'''**), 56.0 (**C1, C1'''**), 55.9, 55.8 (4xO**C**H$_3$), 39.8 (**C3, C3'''**), 27.7 (**C4, C4'''**).

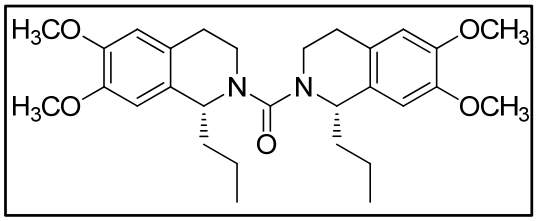
5.2.4.4. Synthesis of (±)-(*R**,*S**)-Bis(1-ethyl-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone 7md.



Obtained according to the general procedure **5.2.4** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluene sulfinic acid (0.18 g, 1.12 mmol, 2.2 equiv.), propionaldehyde (0.23 g, 2.04 mmol, 4.0 equiv.) and DCM (5.0 mL) as solvent at 45 ºC. Purification by flash column chromatography on silica gel using diethyl ether as eluent afforded the product **7md** (0.16 g, 0.17 mmol) as a white solid in 32 % yield.**; Mp** 154 - 156 ºC; **IR (NaCl) ν_{max}** 3020, 1930 cm^{-1}; **Anal**. Calcd for $C_{27}H_{36}N_2$: C, 69.21; H, 7.74; N, 5.98. Found: C, 69.39; H, 7.51; N, 5.75; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.57 (s, 2H, **H8, H8''**), 6.56 (s, 2H, **H5, H5''**),

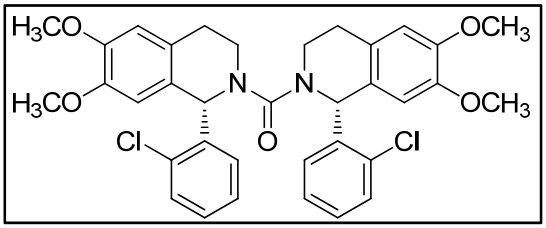
4.71 (dd, *J* = 8.9, 5.2 Hz, 1H, **H1, H1''**), 3.84 (s, 12H, 4xOC**H**$_3$), 3.84 – 3.76* (m, 2H, **H3**), 3.37* (ddd, *J* = 13.4, 11.6, 4.4 Hz, 2H, **H3''**), 2.85** (ddd, *J* = 17.5, 11.4, 6.3 Hz, 2H, **H4**), 2.61** (dd, *J* = 16.3, 2.5 Hz, 2H, **H4''**), 1.86 – 1.66 (m, 4H, **H1', H1'''**), 0.95 (t, *J* = 7.3 Hz, 6H, **H2', H2'''**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.9 (N**C**ON), 147.7, 147.4 (**C6, C6'', C7, C7''**), 130.5 (**C8a, C8a''**), 125.7 (**C5a, C5a''**), 111.5 (**C5, C5''**), 110.0 (**C8, C8''**), 57.3 (**C1, C1''**), 56.1, 56.0 (4xO**C**H_3), 40.4 (**C3, C3''**), 30.0 (**C1', C1'''**), 28.4 (**C4, C4''**), 11.4 (**C3', C3'''**).

5.2.4.5. Synthesis of (±)-(*R**,*S**)-Bis(6,7-dimethoxy-1-propyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone 7me.



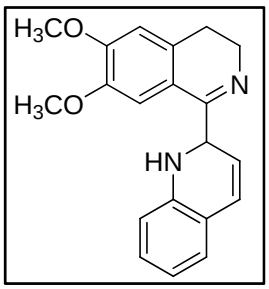
Obtained according to the general procedure **5.2.4** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluene sulfinic acid (0.24 g, 1.53 mmol, 3equiv.), butyraldehyde (0.37 g, 5.1 mmol) and toluene (5.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using diethyl ether eluent afforded the product **7me** (0.15 g, 0.31 mmol) as a white solid in 60 % yield as a mixture of rotamers in $CDCl_3$, 25ºC; **Mp** 66 – 68 ºC; **IR (NaCl) ν_{max}** 3072, 1910 cm^{-1}; **Anal.** Calcd for $C_{29}H_{40}N_2$: C, 70.13; H, 8.12; N, 5.64. Found: C, 70.00; H, 8.10; N, 5.46; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.55* (s, 2H, **H5, H8,**), 6.53* (s, 2H, **H5'', H8''**) 5.03 – 4.27 (m, 2H, **H1, H1''**), 3.92 – 3.70** (m, 14H, 4xOC**H**$_3$, **H3**), 3.37** (m, 2H, **H3''**), 2.92 – 2.58$^{\#}$ (m, 2H, **H4**), 2.34$^{\#}$ (m, 2H, **H4''**), 1.87 – 1.56 (m, 4H, **H1', H1'''**), 1.44 – 1.20 (m, 4H, **H2', H2'''**), 0.89 (t, *J* = 7.1 Hz, 6H, **H3', H3'''**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.6, 164.5 (N**C**ON), 148.1, 147.7, 147.6, 147.4, 147.3, 147.0 (4xO**C**H_3), 130.7, 130.6, 125.6, 125.5 **(C4a, C8a, C4a'', C8a''**), 111.6, 111.5, 111.3, 110.3, 110.0, 109.9 **(C5, C8, C5'', C8''**), 56.2, 56.0, 55.9, 55.9 (4xO**C**H_3), 55.7 (**C1, C1''**), 40.1 (**C3, C3''**), 39.3, 39.1 (**C1', C1'''**), 28.2, 27.6, 26.4 (**C4, C4''**), 20.1, 20.0, 19.9 (**C2', C2'''**), 14.2, 14.1, 14.0 (**C3', C3'''**).

5.2.4.6. Synthesis of ((R*)-1-(2-chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)((S*)-1-(2-chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone 7mf.



Obtained according to the general procedure **5.2.4** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluene sulfinic acid (0.24 g, 1.53 mmol, 3equiv.), 4-chlorobezanzaldehyde (0.22 g, 1.52 mmol) and toluene (5.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using 5:5 petroleum ether:diethyl ether eluent afforded the product **7mf** (0.28 g, 0.11 mmol) as a white solid in 56 % yield; **Mp** 225 – 226 ºC; **IR (NaCl)** ν_{max} 3070, 1940 cm^{-1}; **Anal.** Calcd for $C_{35}H_{34}Cl_2N_2$: C, 66.35; H, 5.41; N, 4.42. Found: C, 66.20; H, 5.30; N, 4.46.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.8, 1.3 Hz, 2H, **H3', H3'''**), 7.19 (td, *J* = 7.6, 1.8 Hz, 2H, **H4', H4'''**), 7.09 (td, *J* = 7.5, 1.4 Hz, 1H, **H5', H5'''**), 6.81 (dd, *J* = 7.6, 1.7 Hz, 1H, **H6', H6'''**), 6.61* (s, 2H, **H5, H8**), 6.54 (s, 1H, **H1**, **H1''**), 6.40* (s, 2H, **H5'', H8''**), 3.87 (s, 6H, 2xOC**H$_3$**), 3.70 (s, 6H, 2xOC**H$_3$**), 3.59 – 3.47** (m, 2H, **H4**), 3.29 – 3.13** (m, 2H, **H4''**), 3.06 – 2.92# (m, 1H, **H3**), 2.71 – 2.50# (m, 2H, **H3''**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 163.5 (N**C**ON), 148.1, 147.7 (4x**C** - OCH_3), 141.2 (**C1', C1'''**), 134.7 (**C2', C2'''**), 131.4 (**C6', C6'''**), 129.9 (**C3', C3'''**), 128.6 (**C4', C4'''**), 127.0, 126.9 (**C4a, C8a, C4a'', C8a''**), 126.3 (**C5', C5'''**), 111.1, 110.9 (**C5, C8, C5'', C8''**), 56.0, 55.9 (4xO**C**H_3), 55.2 (**C1, C1''**), 42.5 (**C3, C3''**), 28.2 (**C4, C4''**).

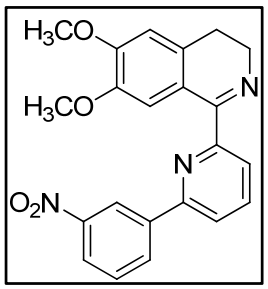
5.2.5. Synthesis of 2-(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)-1,2-dihydroquinoline 7na.



Obtained according to the general procedure **5.2.4** using the compound **3** (0.20 g, 0.51 mmol) as starting material, sulfuric acid 98 % (0.092 g, 0.94 mmol, 1.8 equiv.), 1,2-dihydroquinoline-2-carbaldehyde (0.21 g, 1.52 mmol) and AcOH (2.0 mL) as solvent at 80 ºC. Purification by flash column chromatography on silica gel using diethyl ether as eluent afforded the product **7na** (0.16 g, 0.19 mmol) as a brown solid in 99 % yield; **Mp** 73 – 75 ºC; **IR (NaCl)** ν_{max} 3070, 1519 cm^{-1}; **Anal**. Calcd for $C_{20}H_{20}N_2$: C, 66.82; H, 4.98; N, 10.39. Found: C, 66.70; H, 4.86; N, 10.19.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.6 Hz, 1H, **H3'**), 8.13 (d, *J* = 8.4 Hz, 1H, **H8'**), 8.02 (d, *J* = 8.5 Hz, 1H, **H7'**), 7.84 (d, *J* = 7.3 Hz, 1H, **H6'**), 7.71 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H, **H4'**), 7.55 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H, **H5'**), 7.39 (s, 1H, **H8**), 6.75 (s, 1H, **H5**), 4.09 – 3.83 (m, 2H, **H3**), 3.92 (s, 3H, O**C**H_3),

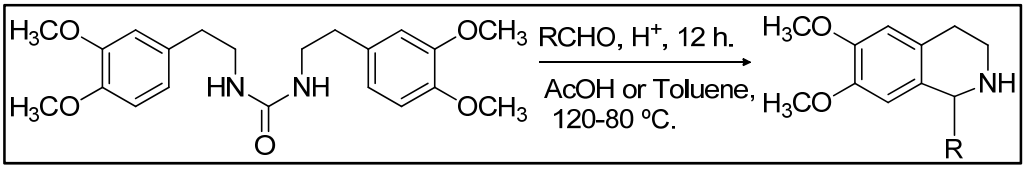
3.74 (s, 3H, OC**H**$_3$), 2.99 – 2.45 (m, 2H, **H4**).; ^{13}**C NMR** (63 MHz, $CDCl_3$) δ 164.9 (**C1**), 157.0 (**C1'**), 151.0 (**C6**), 147.0, 146.9 (**C2a', C7**), 136.7 (**C3'**), 132.5 (**C4a**), 129.8, 129.7 (**C8', C4'**), 128.0 (**C6a'**), 127.6 (**C6'**), 127.1 (**C5'**), 121.3 (**C7'**), 120.8 (**C8a**), 112.4 (**C8**), 110.1 (**C5**), 56.0 (2xO**C**H_3), 48.0 (**C3**), 25.9 (**C4**).

5.2.6. Synthesis of 6,7-dimethoxy-1-(6-(3-nitrophenyl)pyridin-2-yl)-3,4-dihydroisoquinoline 7nb.



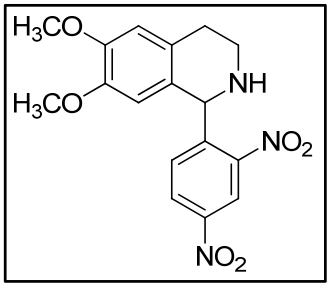
Obtained according to the general procedure **5.2.4** using the compound **3** (0.20 g, 0.51 mmol) as starting material, sulfuric acid 98 % (0.092 g, 0.94 mmol, 1.8 equiv.), 6-(3-nitrophenyl)picolinaldehyde (0.35 g, 1.52 mmol) and AcOH (2.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using ethyl acetate as eluent afforded the product **7nb** (0.075 g, 0.19 mmol) as a pale orange solid in 20 % yield; **Mp** 139 – 140 ºC; **IR (NaCl)** ν_{max} 3076, 1945, 1340, 1519 cm^{-1}; **Anal**. Calcd for $C_{22}H_{19}N_3$: C, 67.86; H, 4.92; N, 10.79. Found: C, 67.76; H, 4.86; N, 10.89.; ^{1}**H NMR** (250 MHz, $CDCl_3$) δ 8.87 (t, *J* = 1.9 Hz, 1H, **H2''**), 8.51 – 8.34 (m, 1H, **H6''**), 8.23 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H, **H4''**), 7.99 – 7.85 (m, 3H, **H4', H5', H6'**), 7.61 (t, *J* = 8.0 Hz, 1H, **H5''**), 7.33 (s, 1H, **H8**), 6.79 (s, 1H, **H5**), 3.95 (s, 3H, OC**H**$_3$), 3.94 – 3.85 (m, 2H, **H3**), 3.74 (s, 3H, OC**H**$_3$), 2.85 – 2.72 (m, 2H, **H4**).; ^{13}**C NMR** (63 MHz, $CDCl_3$) δ 164.6 (**C1**), 157.7 (**C1'**), 153.0 (**C3'**), 151.2 (**C**-OCH_3), 148.9 (**C3''**), 147.1 (**C**-OCH_3), 140.8 (**C1''**), 138.2* (**C5'**), 132.8 (**C6''**), 132.6 (**C4a**), 129.9 (**C5''**), 123.8 (**C4''**), 123.6* (**C4'**), 121.6 (**C2''**), 120.8 (**C8a**), 120.6*(**C6'**), 112.2 (**C8**), 110.2 (**C5**), 56.2, 56.1 (2xOC**H**$_3$), 48.0 (**C3**), 26.0 (**C4**).

5.2.7. General procedure to obtained 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 7oa – 7oc.



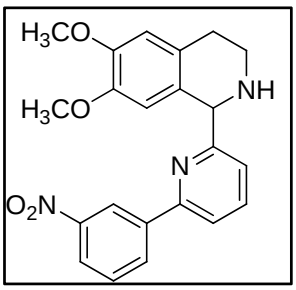
To a solution of compound **3** (1.0 equiv.) in AcOH or toluene (5.0 mL) was added aryl or alkyl aldehyde (3 equiv.), sulfuric acid or *p*-toluene sulfinic acid (1.8 – 3.0 equiv.) at 120 - 80 ºC for 12 h. The mixture was quenched with a saturate solution of Na_2HCO_3, was extracted with DCM (2x30 mL) and concentrated under reduced pressure. The crude was purified by flash column chromatography using a mixture ethyl acetate: methanol to give the compounds **7oa – 7oc**

5.2.7.1. Synthesis of 1-(2,4-dinitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 7oa.



Obtained according to the general procedure **5.2.7** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluene sulfinic acid (0.24 g, 1.53 mmol, 3equiv.), 2,4-dinitrobenzaldehyde (0.30 g, 1.50 mmol) and toluene (5.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using 9:1 ethyl acetate: methanol eluent afforded the product **7oa** (0.03 g, 0.08 mmol) as a black oil in 16 % yield; **IR (NaCl) ν_{max}** 3106, 1940, 1340, 1519 cm^{-1}; **Anal**. Calcd for $C_{17}H_{17}N_3$: C, 56.82; H, 4.77; N, 10.69 Found: C, 57.96; H, 4.66; N, 10.69.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.67 (d, *J* = 2.3 Hz, 1H, **H3'**), 8.25 (dd, *J* = 8.6, 2.3 Hz, 1H, **H5'**), 7.34 (d, *J* = 8.6 Hz, 1H, **H6'**), 6.67 (s, 1H, **H5**), 6.19 (s, 1H, **H8**), 5.66 (s, 1H, **H1**), 3.88 (s, 3H, OC**H$_3$**), 3.87 – 3.81 (m, 1H, N**H**), 3.68 (s, 3H, OC**H$_3$**), 3.07 – 2.96 (m, 2H, **H3**), 2.82 (dd, *J* = 11.2, 5.6 Hz, 2H, **H4**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 150.1, 148.6, 147.7, 146.8, 145.9 (**C6, C7, C1', C2', C4'**), 133.5 (**C5'**), 128.5* (**C4a**), 126.3 (**C6'**), 126.1* (**C8**), 119.8 (**C3'**), 111.9 (**C5**), 110.6 (**C8a**), 56.1 (**C1**), 56.0, 55.0 (2xOC**H$_3$**), 40.4 (**C3**), 28.9 (**C4**).

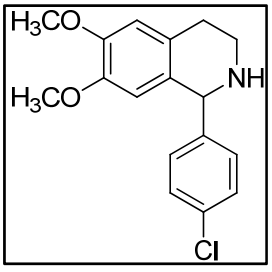
5.2.7.2. Synthesis of 6,7-dimethoxy-1-(6-(3-nitrophenyl)pyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline 7ob.



Obtained according to the general procedure **5.2.7** using the compound **3** (0.20 g, 0.51 mmol), sulfuric acid 98 % (0.092 g, 0.94 mmol, 1.8 equiv.), 6-(3-nitrophenyl)picolinaldehyde (0.35 g, 1.52 mmol) as starting material and AcOH (2.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using diethyl ether as eluent afforded the product

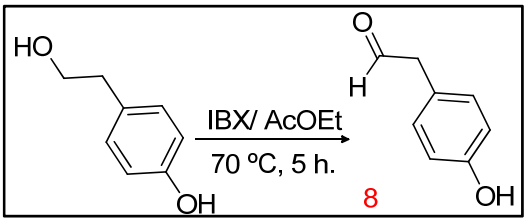
7ob (0.039 g, 0.01 mmol) as a brown solid in 38 % yield; **Mp** 98 – 100ºC; **IR (NaCl) ν_{max}** 3156, 1972, 1519 cm^{-1}; **Anal**. Calcd for $C_{22}H_{21}N_3$: C, 67.51; H, 5.41; N, 10.74. Found: C, 67.53; H, 5.42; N, 10.60; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.88 (t, 1H, **H2''**), 8.39 (dd, *J* = 7.8, 0.9 Hz, 1H, **H6**''), 8.27 – 8.17 (m, 1H, **H4''**), 7.79 – 7.68 (m, 2H, **H5', H6'**), 7.60 (d, *J* = 8.1 Hz, 1H, **H5''**), 7.16 (dd, *J* = 6.9, 1.6 Hz, 1H, **H4'**), 6.66 (s, 1H, **H5**), 6.45 (s, 1H, **H8**), 5.30 (s, 1H, **H1**), 3.86 (s, 3H, OC**H$_3$**), 3.68 (s, 3H, OC**H$_3$**), 3.28 – 3.01 (m, 2H, **H3**), 3.01 – 2.77 (m, 2H, **H4**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 163.8 (**C1'**), 154.1 (**C3'**), 148.8 (**C3''**), 148.0, 147.2 (2x**C**-OCH_3), 140.9 (**C1''**), 137.7 (**C5', C6'**), 132.8 (**C6''**), 129.8 (**C5''**), 127.7, 127.5 (**C4a, C8a**), 123.6 (**C4''**), 122.6 (**C4'**), 121.9 (**C2''**), 119.2 (**C5', C6'**), 111.7 (**C5**), 110.9 (**C8**), 61.9 (**C1**), 56.0, 55.9 (2xO**C**H_3), 41.0 (**C3**), 29.0 (**C4**).

5.2.7.3. Synthesis of 1-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 7oc.



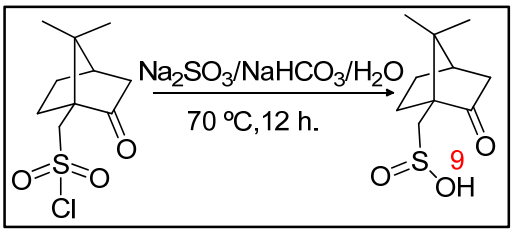
Obtained according to the general procedure **4.2.7** using the compound **3** (0.20 g, 0.51 mmol) as starting material, *p*-toluene sulfinic acid (0.24 g, 1.53 mmol, 3equiv.), 4-chlorobenzaldehyde (0.22 g, 1.50 mmol) and toluene (5.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using ethyl acetate eluent afforded the product **7oc** (0.049 g, 0.16 mmol) as a brown solid in 32 % yield; **Mp** 102 – 105ºC; **IR (NaCl) ν_{max}** 3156, 1972, 1519 cm^{-1}; **Anal.** Calcd for $C_{17}H_{18}N$: C, 67.21; H, 5.97; N, 4.61. Found: C, 67.26; H, 5.96; N, 4.60; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2H, **H3', H5'**), 7.17 (d, *J* = 8.5 Hz, 2H, **H2', H6'**), 6.61 (s, 1H, **H5**), 6.17 (s, 1H, **H8**), 3.84 (s, 3H, OC**H$_3$**), 3.79 – 3.73 (m, 1H, N**H**), 3.62 (s, 3H, OC**H$_3$**), 3.21 – 3.10 (m, 1H, **H3**), 3.06 – 2.83 (m, 2H, **H3, H4**), 2.71 (dt, *J* = 9.7, 4.5 Hz, 1H, **H4**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 147.7, 147.1 (2x**C**-OCH_3), 143.4 (**C1'**), 133.0 (**C4'**), 130.3 (**C2', C6'**), 129.2* (**C8a**), 128.5 (**C3', C5'**), 127.6* (**C4a**), 111.4 (**C5**), 110.7 (**C8**), 60.7 (**C1**), 55.8, 55.8 (2xO**C**H_3), 41.8 (**C3**), 29.2 (**C4**).

5.2.8. Synthesis of 4-hydroxybenzaldehyde 8.



A mixture of 4-(2-hydroxyethyl)phenol (0.050 g, 0.36 mmol), IBX (0.15 g, 0.54 mmol) in ethyl acetate (15 mL) was stirred for 5 h at 70 ºC. The reaction was warmed to room temperature, filtered and concentrated *in vacuo*. The mixture was purified by flash column cromatography using a mixture of 8:2 petroleum ether:diethyl ether as eluent to give **8** (0.044 g, 0.32 mmol) 90% yield as a colorless oil; **IR (NaCl) ν_{max}** 3300, 1780 cm^{-1}; **Anal.** Calcd for $C_8H_8O_2$: C, 70.57; H, 5.92. Found: C, 70.41; H, 5.82; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 9.71 (t, *J* = 2.4 Hz, 1H, **H1**), 7.07 (d, *J* = 8.6 Hz, 2H, **H2'**, **H6'**), 6.84 (d, *J* = 8.6 Hz, 2H, **H3'**, **H5'**), 6.76 (s, 1H, -O**H**), 3.62 (d, *J* = 2.4 Hz, 2H, **H2**);**^{13}C NMR** (63 MHz, $CDCl_3$) δ 200.30 (**C**O), 155.37 (**C4'**), 130.97 (**C2', C6'**), 128.15 (**C1'**), 116.08 (**C3'**, **C5'**), 49.82 (**C2**).

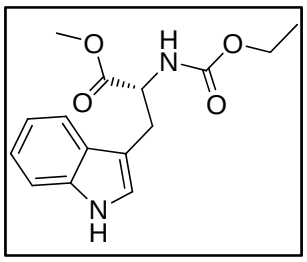
5.2.9. Synthesis of (1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfinic acid 9.



To a stirred solution of Na_2SO_3 (0.56 g, 4.40 mmol) and $NaHCO_3$ (0.60 g, 9.80 mmol) in H_2O (2.0 mL) a solution of (1*S*)-(+)-10-camphorsulfonyl chloride (0.10 g, 0.40 mmol) in acetone (0.5 mL) was added dropwise. The reaction mixture was heated at 70 ºC for 12 h. The white precipitate was filtered and dissolved in a mixture of H_2O (3.0 mL) and diethyl

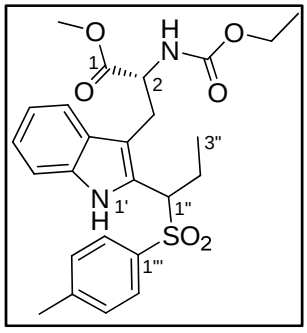
ether (3.0 mL) after the addition of HCl 37 % (0.9 mL) was stirred for 1 h.at room temperature. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a white solid. **Mp**: 110-111 ºC; **IR (NaCl) ν_{max}** 3010, 2300, 1805 cm^{-1}; **Analysis**: Calcd. for $C_{10}H_{16}SO_3$: C, 55.53; H, 7.46; S, 14.82 Found: C, 55.61; H, 7.45; S, 14.67.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.55 (s, 1H, O**H**), 2.95 (d, *J* = 14.0 Hz, 1H, **H1**), 2.79 (d, *J* = 14.0 Hz, 1H, **H1**), 2.44 (ddd, *J* = 18.8, 4.8, 2.3 Hz, 1H, **H3'**), 2.18 – 2.14 (m, 1H, **H6'**), 2.11 – 2.00 (m, 2H, **H4', H3'**), 2.00 – 1.83 (m, 1H, **H6'**), 1.91 – 1.83 (m, 1H, **H5'**), 1.48 – 1.42 (m, 1H, **H5'**), 1.00 (s, 3H), 0.92 (s, 3H).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 219.6 (**C2'**), 60.4 (**C1'**), 56.2 (**C1**), 49.2 (**C7'**), 43.0 (**C4'**), 42.8 (**C3'**), 27.3, 27.0 (**C5', C6'**), 20.1, 19.4 (2x**C**H_3-C7').

5.2.10. Synthesis of (*R* or *S*)-methyl 2-(ethoxycarbonylamino)-3-(1*H*-indol-3-yl)propanoate 10.



To a stirred solution of the commercial available *R* or *S* tryptophan chlorhydrate (1.0 g, 3.9 mmol), and DMAP (0.5 g, 4.1 mmol), ethyl chloroformiate (0.46 mL, 5.9 mmol) and Et_3N (0.58 mL, 3.5 mmol) were added dropwise. Then, the mixture was heated to reflux for 4 hours. The reaction was quenched with 1.0 N HCl and extracted with $CHCl_3$ (2x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a brown oil. The crude was purified by flash column chromatography using a mixture 9:1 ethyl acetate:methanol to give compound **10** (0.96 g, 3.52 mmol) as a brown oil, 90% yield. **Mp** 94–95ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1} **Analysis**: Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 62.00; H, 6.20; N, 9.59. **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.49 (s, 1H, N**H**), 7.54 (dd, *J* = 7.0, 1.1 Hz, 1H, C$\mathbf{H}_{Ar}$), 7.39 – 7.29 (m, 1H, C$\mathbf{H}_{Ar}$), 7.24 – 7.15 (m, 1H, C$\mathbf{H}_{Ar}$), 7.15 – 7.06 (m, 1H, C$\mathbf{H}_{Ar}$), 6.97 (s, 1H, **H**2'), 5.28 (d, *J* = 8.0 Hz, 1H, N**H**COOCH_2CH_3), 4.70 (dt, *J* = 7.9, 5.5 Hz, 1H, **H2**), 4.11 (q, *J* = 7.1 Hz, 2H, NHCOOC**H_2**CH_3), 3.68 (s, 3H, COOC**H_3**), 3.30 (d, *J* = 5.4 Hz, 2H, **H3**), 1.22 (dd, *J* = 8.2, 6.0 Hz, 3H, NHCOOCH_2C**H_3**). **^{13}C NMR** (63 MHz, MeOD) δ 174.5 (**C**OOCH_3), 158.6 (NH**C**OOCH_2CH_3), 138.0, 128.6* (**C3', C3a'**), 124.4, 122.4, 119.8, 119.1, 112.3 (**C**H_{Ar}), 110.7* (**C7a'**), 62.0 (NHCOO**C**H_2CH_3), 56.3 (**C2**), 52.6 (COO**C**H_3), 28.7 (**C3**), 14.9 (OCH_2**C**H_3).

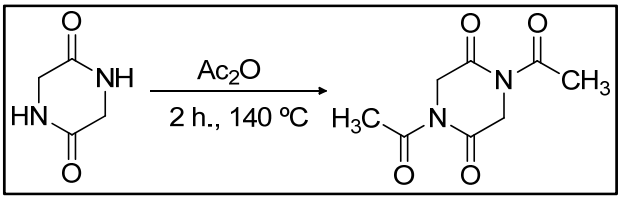
5.2.11. Synthesis of (±) (2*R**)-methyl 2-(ethoxycarbonylamino)-3-(2-(1-tosylpropyl)-1*H*-indol-3-yl)propanoate 11.



Obtained according to the general procedure 1.6 using compound **10** (0.2 g, 0.74 mmol), as starting material, *p*-toluene sulfinic acid (0.13 g, 0.84 mmol), propanaldehyde (6.86 g, 9.4 mmol) and DCM (3.0 mL) as solvent. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **11** (0.26 g, 0.73 mmol) as a clean yellow oil in 99% yield as a mixture of rotamers in $CDCl_3$, 25ºC.;**IR (NaCl) ν_{max}** 3190, 2900, 1693, 1625, cm^{-1}.**Analysis:** Calcd for $C_{25}H_{30}N_2O_6$: C, 61.71; H, 6.21; N, 5.76; O, 19.73; S, 6.59. Found: C, 61.70; H, 6.10; N, 5.69; S, 6.50.**^{1}H NMR** (250 MHz, MeOD) δ 7.42* (dd, *J* = 7.7, 3.1 Hz, 1H, **H4'**), 7.31** (dd, *J* = 8.3, 1.6 Hz, 3H, **H2'''**, **H3'''**, **H5'''**), 7.02 – 6.88** (m, 3H, **H6'''**, **H1**, **H7'**), 6.83* (s, 2H, **H5'**, **H6'**), 5.72 – 5.54 (m, 1H, **H1''**), 4.54 (td, *J* = 8.1, 4.2 Hz, 1H, **H2**), 4.05 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 3.74# (s, 1.5H, $COOCH_3$), 3.69# (s, 1.3H, $COOCH_3$), 3.63# (s, 0.3H, $COOCH_3$), 3.29 (dd, *J* = 17.0, 7.9 Hz, 1H, **H3**), 3.20 – 3.03 (m, 1H, **H3**), 2.70 – 2.50 (m, 1H, **H2''**), 2.45 – 2.31 (m, 1H, **H2''**), 2.16 (s, 1.5H, CH_3-Ar), 2.14 (s, 1.5H, CH_3-Ar), 1.18 (td, *J* = 6.9, 2.9 Hz, 3H, OCH_2CH_3), 0.84 (td, *J* = 7.0, 3.1 Hz, 3H, **H3''**).**^{13}C NMR** (63 MHz, MeOD) δ 174.1, 174.0 (**C1**), 158.5, 158.4 ($NHCOOCH_3$), 146.5, 146.4 (**C1'''**), 139.0, 134.5, 134.4, 130.7* (**C4'''**, **C2'**, **C3'**, **C7a'**), 130.5, 130.4, 130.0, 129.9 (**C2'''**, **C3'''**, **C5'''**, **C6'''**), 125.7* (**C3a'**), 123.1, 120.9, 119.7, 119.4, 119.2, 110.0 (**C4'**, **C5'**, **C6'**, **C7'**), 76.7 (**C1''**), 62.1, 62.0 (OCH_2CH_3), 56.1, 56.0 (**C2**), 52.9, 52.8 ($COOCH_3$), 28.6 , 28.3 (**C3**), 21.4, 21.3 (Ar-CH_3), 20.9, 20.8 (**C2''**), 14.9 (OCH_2CH_3), 9.9, 9.8 (**C3''**).

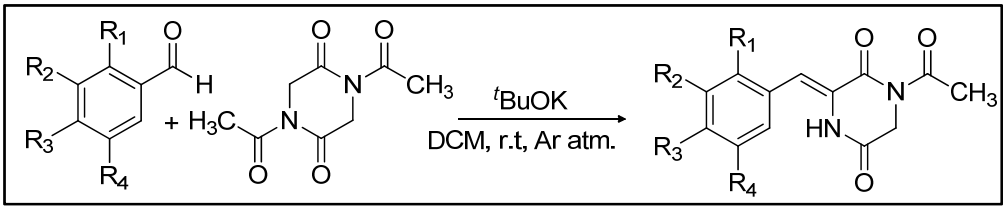
5.3. Strategy core ACE-D-B. Study of tetrahydroisoquinoline, core AC-B.

5.3.1. Synthesis of 1,4-diacetylpiperazine-2,5-dione 13[180].



To glycine anhydride (10.0 g, 88.0 mmol) was added acetic anhydride (156 mL) and the reaction mixture was heated at 140 ºC for 2 h. The solution was concentrated to 75% under reduced pressure and was cooled to room temperature to obtain a dark brown oil. Then solution diethyl ether (40 mL) was added and precipitated was filtered and was washed with diethyl ether (3 x 20 mL) to give compound **13** (16.9 g, 85.0 mmol) in 96% yield as a pale yellow solid.

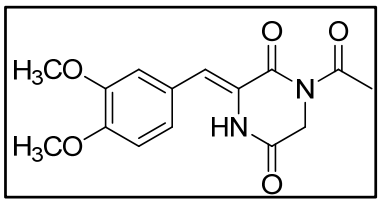
5.3.2. General procedure to obtain (Z)-1-acetyl-3-benzylidenepiperazine-2,5-diones 14a-14b.



To a stirred mixture of compound **13** (1.1 eq) and dimethoxybenzaldehyde (1.0 eq) under an Ar atmosphere, dry DCM (25-50 mL) was added. Over the resulting solution, was added *via* syringe a solution of ^{t}BuOK (1.0 M, 1.0 eq) and the mixture was stirred at room temperature for 12 h. During this time, a bright yellow solid appears. After filtered, the solid was washed with 2.0 N aqueous ammonium chloride solution, distilled water (2 x 10 mL) and diethyl ether (3 x 10 mL) to give compounds **14a-14b** as deep yellow solids.

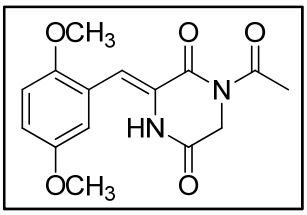
[180] Gallina, C.; Liberatori, A.; *Tetrahedron*. **1974**, *30*, 667.

5.3.2.1. Synthesis of (*Z*)-1-acetyl-3-(3,4-dimethoxybenzylidene)piperazine-2,5-dione 14a.



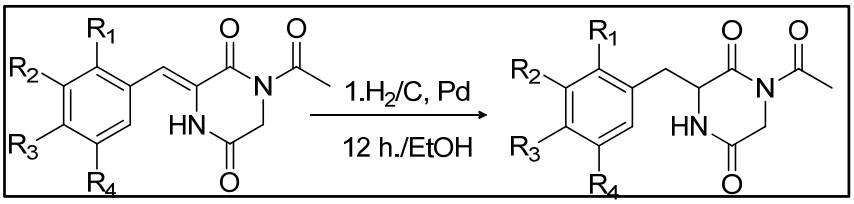
According to the general procedure **4.2.2** using compound **13** (10.0 g, 0.050 mmol), 3,4-dimethoxybenzaldehyde (7.64 g, 0.046 mmol) as starting materials, 1.0 M ^{t}BuOK (50 mL) and DCM (50 mL) as solvent, product **14a** was obtained (13.3 g, 0.043 mmol) as a deep yellow solid in 93% yield. **Mp** 190–191 ºC; **IR (NaCl) ν_{max}** 3100, 2930, 1693, 1625 cm^{-1}; **Analysis:** Calcd**.** for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.21 Found: C, 59.29; H, 5.24; N, 9.30; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.09 (s, 1H, N**H**), 7.11* (s, 1H, **H2'**), 7.03** (d, *J* = 8.0 Hz, 1H, **H5'**), 6.91** (d, *J* = 8.3 Hz, 1H, **H5'**), 6.86* (s, 1H, C**H**-C6), 4.49 (s, 2H, **H3**), 3.90 (d, *J* = 5.8 Hz, 6H, 2 x OC**H$_3$**), 2.63 (s, 3H, COC**H$_3$**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 172.6, 163.0, 160.4 (**C1, C4,** COCH_3), 150.2, 149.7 (2 x **C**-OCH_3), 125.2, 124.5 (**C6, C1'**), 121.5, 120.5, 112.0, 111.7 (**C**H-C6, **C2', C5', C6'**), 56.1 (O**C**H_3), 46.2 (**C3**), 27.3 (CO**C**H_3).

5.3.2.2. Synthesis of (*Z*)-1-acetyl-3-(2,5-dimethoxybenzylidene)piperazine-2,5-dione 14b.



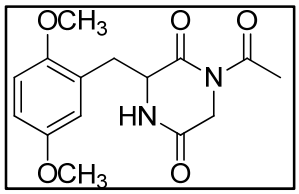
According to the general procedure **4.3.2** using compound **13** (5.0 g, 0.025 mmol), 3,4-dimethoxybenzaldehyde (3.82 g, 0.023 mmol) as starting materials, 1.0 M ^{t}BuOK (25.0 mL) and DCM (25 mL) as solvent, product **14b** was obtained (7.0 g, 0.023 mmol) as a deep yellow solid in 99% yield; **Mp** 191–192 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis:** Calcd. for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.21 Found: C, 63.46; H, 6.36 ; N, 7.00; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.09 (s, 1H, C**H**-C6), 6.95-6.90 (m, 3H, **H3', H4', H6'**), 6.82 (s, 1H, N**H**), 4.48 (s, 2H, **H3**), 3.89 (s, 3H, OC**H$_3$**), 3.78 (s, 3H, OC**H$_3$**), 2.65 (s, 3H, C**H**$_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 172.8 (**C**OCH_3), 162.7, 160.5 (**C1, C4**), 154.2, 150.5 (**C2', C5'**), 126.1, 122.7 (**C6, C1'**), 117.4, 116.5, 116.3 (**C3', C4', C6'**), 113.7 (**C**H-C6), 56.9, 55.9 (2 x O**C**H_3), 46.3 (**C3**), 27.4 (**C**H_3).

5.3.3. General procedure to obtain 1-acetyl-3-benzylpiperazine-2,5-dione 15a-15b.



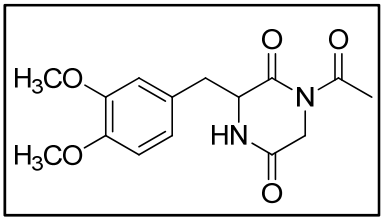
To a solution of **14a–14b** (1.0 eq) in EtOH (75 mL) under an Ar atmosphere, 10% Pd/C (0.1 *w/w*) was added. The mixture was evacuated and back-filled with H_2 (1 atm), and was stirred at room temperature for 12 h. Then, the mixture was filtered through celite, washed with DCM (3 x 30 mL), and evaporated *in vacuo* to obtain compounds **15a–15b** as white solids.

5.3.3.1. Synthesis of 1-acetyl-3-(2,5-dimethoxybenzyl)piperazine-2,5-dione 15a.



According to the general procedure **4.3.3**, using compound **14b** (2.00 g, 6.5 mmol) as starting material, 10 % Pd/C (0.2 g), and EtOH (75 mL) as solvent, compound **15a** was obtained (1.97 g, 6.40 mmol) as a white solid in 98% yield; **Mp** 134-135ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{15}H_{18}N_6O_5$: C, 58.82; H, 5.92; N, 9.15 Found: C, 58.80; H, 5.96; N, 9.00; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.86-6.69 (m, 4H, **H3'', H4'', H6''**, N**H**), 4.40-4.31 (m, 1H, **H6**), 4.16 (d, *J* = 17.8 Hz, 1H, **H3**), 4.00 (d, *J* = 17.8 Hz, 1H, **H3**), 3.76 (s, 3H, O**CH$_3$**), 3.71 (s, 3H, O**CH$_3$**), 3.32 (dd, *J* = 13.7, 4.7 Hz, 1H), 3.03 (dd, *J* = 13.7, 7.7 Hz, 1H), 2.57 (s, 3H, **CH$_3$**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 171.9 (**C**OCH$_3$), 168.7, 166.7 (**C1, C4**), 153.8, 151.8 (**C2', C5'**), 124.2 (**C1'**), 118.0, 113.3, 111.6 (**C3', C4', C6'**), 57.1 (**C6**), 55.9, 55.8 (2 x O**C**H$_3$), 46.0 (**C3**), 33.4 (**C1'**), 27.3 (**C**H$_3$).

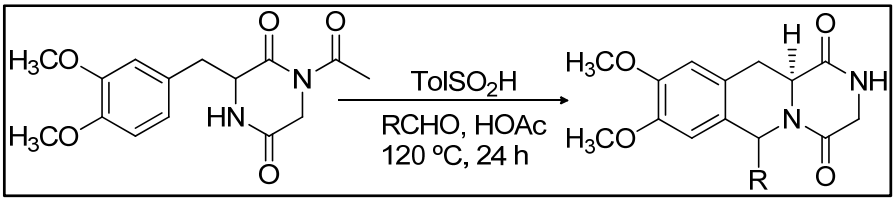
5.3.3.2. Synthesis of 1-acetyl-3-(3,4-dimethoxybenzyl)piperazine-2,5-dione 15b.



According to the general procedure **4.3.3** using compound **14a** (3.00 g, 9.8 mmol) as starting material, 10 % Pd/C (0.35 g), and EtOH (75 mL) as solvent, compound **15b** was obtained (2.80 g, 9.1 mmol) as a white solid in 93% yield. **Mp** 132–133 ºC; **IR (NaCl)**

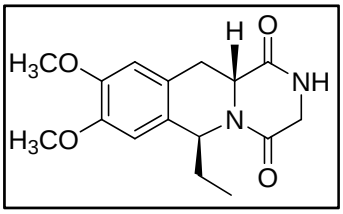
ν_{max} 3200, 2930, 1693, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{15}H_{18}N_2$: C, 58.82; H, 5.92; N, 9.15 Found: C, 59.00; H, 5.80; N, 9.19; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.05 (s, 1H, N**H**), 6.80 (d, *J* = 8.1 Hz, 1H, **H5'**), 6.72 (d, *J* = 1.9 Hz, 1H, **H2'**), 6.67 (dd, *J* = 6.1, 1.8 Hz, 1H, **H6'**), 4.35 (ddd, *J* = 7.0, 4.6, 2.5 Hz, 1H, **H6**), 4.21 (d, *J* = 18.2 Hz, 1H, **H3**), 3.88 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.37 (d, *J* = 18.2 Hz, 1H, **H3**), 3.12 (dd, *J* = 5.3, 3.3 Hz, 2H, CH_2-C6), 2.57 (s, 3H, $COCH_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 171.8, 168.6, 166.8 (**C1, C4,** $COCH_3$), 149.4, 148.9 (2 x **C**-OCH_3), 126.6 (**C1'**), 122.0 (**C6'**), 112.7, 111.6 (**C2', C5'**), 58.2 (**C6'**), 56.0, 56.0 (2xOCH_3), 45.5 (**C3**), 39.9 (CH_2-C6), 27.4 ($COCH_3$).

5.3.4. General procedure to obtain 8, 9-dimethoxy-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 16a–16c.



To a solution of **15a-15b** (1.0 eq) in acetic acid (1.0-2.0 mL) *p*-toluenesulfinic acid (1.1 eq) and the alkyl or aryl aldehyde (2.1eq) were added. The reaction was heated at 120 ºC for 24 h. The mixture was quenched by addition of saturated aqueous solution of $NaHCO_3$ and was extracted with DCM (2 x 20 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give **16a–16c** as brown oils that were purified by silica gel column cromatography using a mixture of ethyl acetate:methanol as eluent.

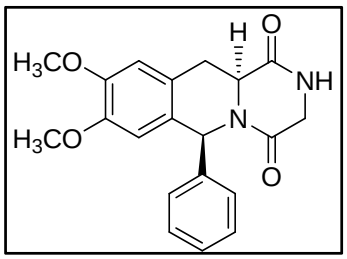
5.3.4.1. Synthesis of 6-ethyl-8,9-dimethoxy-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 16a.



Obtained according to the general procedure **4.3.4** using compound **15b** (0.1 g, 0.32 mmol) and 1-propanaldehyde (0.050 mL, 0.68 mmol) as starting materials, *p*-toluene sulfinic acid (0.056 g, 0.36 mmol) and acetic acid (1.0 mL) as solvent. Purification by flash column chromatography

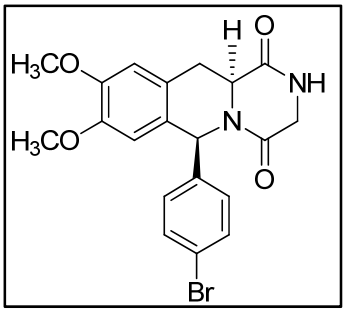
(1:9 ethyl acetate:methanol) afforded product **16a** (0.062 g, 0.202 mmol) as a brown solid in 62% yield; **Mp** 69–70 ºC; **IR (NaCl) ν_{max}** 3150, 2950, 1645, 1605 cm^{-1}; **Analysis**: Calcd. for $C_{16}H_{20}N_2$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.00; H, 6.80; N, 9.29; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.19 (s, 1H, N**H**), 6.60* (s, 1H, **H10**), 6.57* (s, 1H, **H7**), 5.56 (dd, *J* = 10.2, 4.0 Hz, 1H, **H6**), 4.32 (dd, *J* = 11.9, 3.7 Hz, 1H, **H11a**), 4.11 (s, 2H, **H3**), 3.84 (s, 3H, OC**H$_3$**), 3.84 (s, 3H, OC**H$_3$**), 3.22 (dd, *J* = 15.9, 4.0 Hz, 1H, **H11**), 3.03-2.91 (m, 1H, **H11**), 1.93-1.73 (m, 2H, **H1'**), 1.00 (t, *J* = 7.3 Hz, 3H, **H2'**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 168.1, 162.3 (**C1, C4**), 148.2 (2 x **C**-OCH_3), 128.3, 123.1 (**C6a, C10a**), 111.3, 109.8 (**C7, C10**), 56.1, 56.0 (2xO**C**H_3), 53.6 (**C11a**), 51.9 (**C6**), 44.8 (**C3**), 33.2 (**C11**), 29.0 (**C1'**), 11.1 (**C2'**).

5.3.4.2. Synthesis of 8,9-dimethoxy-6-phenyl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 16b.



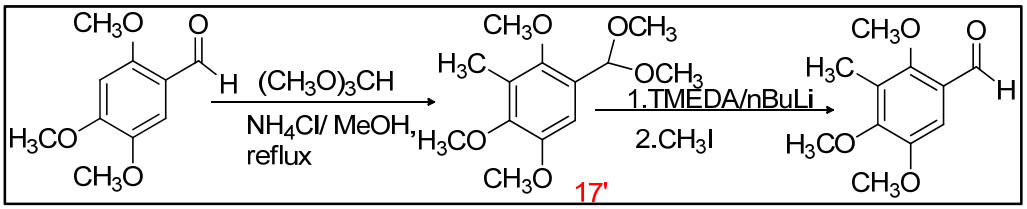
Obtained according to the general procedure **4.3.4** using compound **15b** (0.1 g, 0.32 mmol) and benzaldehyde (0.066 mL, 0.68 mmol, 2.0 eq) as starting materials, *p*-toluene sulfinic acid (0.056 g, 0.36 mmol) and acetic acid (2.0 mL) as solvent. Purification by flash column chromatography using methanol as eluent afforded product **16b** (0.018 g, 0.045 mmol) as a pale yellow solid in 14% yield as a 1:1 mixture of amide rotamers in $CDCl_3$, 25 ºC; **Mp** 140-142 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{20}H_{20}N_2$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.00; H, 5.80; N, 7.91; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.84-6.62 (m, 7H, C**H$_{Ar}$**), 4.22 (bs, 1H, **H6**), 3.85 (s, 1.5H, OC**H$_3$**), 3.84 (s, 1.5H, OC**H$_3$**), 3.83 (s, 1.5H, OC**H$_3$**), 3.82 (s, 1.5H, OC**H$_3$**), 3.73 (d, *J* = 5.0 Hz, 1H, **H11a**), 3.69-3.61 (m, 1H, **H3**), 3.23 (d, *J* = 17.6 Hz, 1H, **H3**), 3.13-3.00 (m, 2H, **H11**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 172.0, 170.9, 167.0, 166.3 (**C1, C4**), 149.4, 149.2, 149.0, 148.7, 148.6, 148.3 (2 x OCH_3), 128.1, 127.7, 127.1 (**C6a, C10a, C1'**), 122.3, 122.0, 121.5 (**C2', C3', C4', C5', C6'**), 112.9, 112.4, 111.5, 111.3 (**C7, C10**), 56.5, 56.4 (**C6**), 56.1, 56.0, 56.0, 55.9, 55.9, 53.5, 52.6 (**C11a**), 44.6, 43.2 (**C3**), 39.9, 37.5 (**C11**).

5.3.4.3. Synthesis of 6-(4-bromophenyl)-8,9-dimethoxy-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 16c.



Obtained according to the general procedure **4.3.4** using compound **15b** (0.063 g, 0.20 mmol) and 4-bromobenzaldehyde (0.12 g, 0.65 mmol) as starting materials, *p*-toluene sulfinic acid (0.056 g, 0.36 mmol), and acetic acid (2.0 mL) as solvent. Purification by flash column chromatography using methanol as eluent afforded product **16c** (0.011 g, 0.023 mmol) as a pale yellow solid in 11% yield. **Mp** 149-150 ºC; **IR (NaCl) ν_{max}** 3200, 2980, 1690, 1620 cm^{-1}; **Analysis**: Calcd. for $C_{20}H_{19}N_2$: C, 55.70; H, 4.44; N, 6.50. Found: C, 55.60; H, 4.62; N, 6.59; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.92* (d, *J* = 8.4 Hz, 2H, **H2', H6', H3', H5'**), 7.60* (d, *J* = 8.4 Hz, 2H, **H2', H6', H3', H5'**), 7.17-6.77 (m, 3H, N**H, H7, H10**), 6.74 (s, 1H, **H6**), 4.28 (s, 1H, **H11a**), 3.85 (s, 3H, OC**H$_3$**), 3.83 (s, 3H, OC**H$_3$**), 3.69 (d, *J* = 17.4 Hz, 1H, **H3**), 3.24 (d, *J* = 17.6 Hz, 1H, **H3**), 3.19-2.97 (m, 2H, **H11**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 168.5, 166.6 (**C1, C4**), 149.3, 148.7 (**C8, C9**), 132.0* (**C2', C6'**), 131.8 (**C1'**), 131.7* (**C3', C5'**), 128.9, 128.7, 126.9 (**C6a, C10a, C4'**), 112.9, 111.5 (**C7, C10**), 56.5, 56.4 (**C6, C11a**), 56.0 (2 x OCH_3), 44.5 (**C3**), 40.0 (**C11**).

5.3.5. Synthesis of 2,4,5-trimethoxy-3-methylbenzaldehyde 17[181].

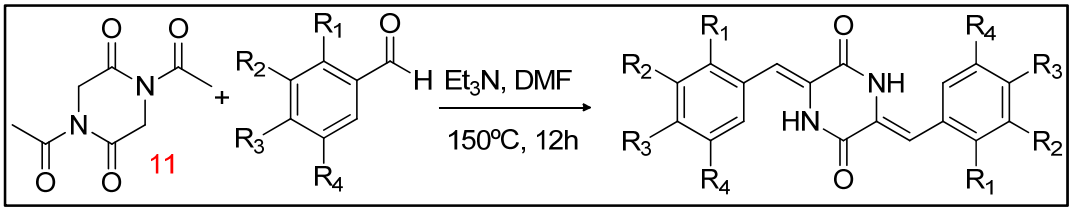


To a solution of 2,4,5-trimethoxylbenzaldehyde (20.0 g, 0.102 mol) and ammonium chloride (0.30 g, 5.60 mmol) in dry methanol (120 mL) under Ar atmosphere, trimethyl orthoformate (39.2 mL, 0.27 mol) was added and the mixture was reflux for 3 h. Then, the reaction was quenched with a solution of Et_3N (3.0 mL) in H_2O (100 mL) and was extracted with AcOEt (3 x 30 mL). The organic layer was washed with a saturated solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give

[181] Gonzalez J. F.; De la Cuesta, E.; Avendaño, C. *Synth. Commun.*,**2004**, *34*, 1589.

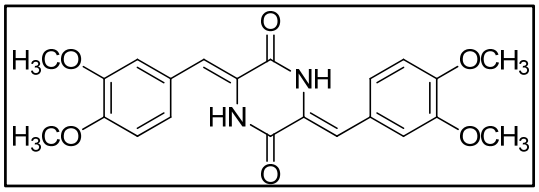
compound **17'** (22.0 g, 0.091 mol) as a red-brown solid in 89% yield. Then, to a solution of **17'** (5.0 g, 0.021 mol) in dry THF (20 mL) under Ar atmosphere at -78 ºC, TMEDA (4.1 mL, 0.027 mol) and 1.6 M *n*BuLi (16.0 mL, 0.026 mol) were added and the solution was stirred for 1 h. After adding methyl iodide (1.5 mL, 0.024 mol) the solution was warmed to room temperature and stirred for 12 h more. The mixture was washed with a solution of 1.0 N HCl, extracted with DCM (3 x 30 mL), dried over anhydride Na_2SO_4, filtered and evaporated *in vacuo*. The crude was purified by flash column chromatography with a mixture of 9:1 petroleum ether:diethyl ether as eluent to obtain compound **17** (4.26 g, 0.020 mmol) as a pale yellow solid in 97% yield. Compound **17** was kept at -25 ºC.

5.3.6. General procedure to obtain (3*Z*, 6*Z*)-dimethoxy-3,6-dibenzylidenepiperazine-2,5-dione 18a–18b.



To compound **13** (1.0 eq), dimethoxybenzaldehyde (2.35 eq), Et_3N (3.00 eq) and DMF (1.30 eq) were added. The reaction mixture was stirred at 150 ºC for 24 h and then, the bright yellow solid was washed with distilled water (3 x 25 mL), ethyl acetate (3 x 10 mL) and diethyl ether (2 x 15 mL) to give compounds **18a–18b** as deep yellow solids.

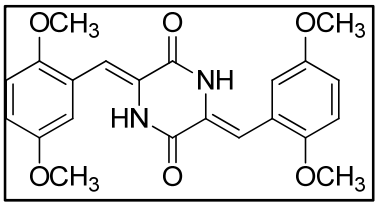
5.3.6.1. Sythesis of (3Z,6Z)-3,6-bis(3,4-dimethoxybenzylidene)piperazine-2,5-dione 18a.



According to the general procedure **4.3.6** using compound **13** (10.0 g, 0.050 mol), 3,4-dimethoxybenzaldehyde (19.53 g, 0.12 mol) and Et_3N (20.5 mL) as starting material and DMF (5.0 mL) as solvent, product **18a** was obtained (18.3 g, 0.043 mol) as a deep yellow solid in 86% yield. **Analysis**: Calcd. for $C_{22}H_{22}N_2O_6$: C 64.38, H 5.40, N 6.83. Found C 64.28, H 5.42, N 6.79. **Mp**: 294-296 ˚C. **IR (NaCl) ν_{max}**: 3193, 1680, 1627, 1245 cm^{-1}. **^{1}H-RMN** (250MHz,

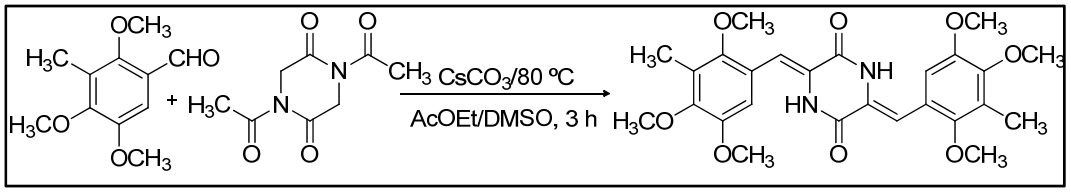
$CDCl_3$) δ: 8.22 (s, 1H, N**H**), 7.06 (dd, 1H, *J* = 8.6 y 1.9 Hz, **H6'**), 6.99 (s, 1H, C**H**-C3), 6.97 (d, 1H, *J* = 8.6 Hz, **H5'**), 6.89 (d, 1H, *J* = 1.9 Hz, **H2'**), 3.96 (s, 3H, OC**H$_3$**), 3.94 (s, 3H, OC**H$_3$**).

5.3.6.2. Synthesis of (3*Z*,6*Z*)-3,6-bis(2,5-dimethoxybenzylidene)piperazine-2,5-dione 18b.



According to the general procedure **4.3.2** using compound **13** (20.0 g, 0.100 mol) and 3,4-dimethoxybenzaldehyde (39.56 g, 0.24 mol) as starting materials, Et_3N (40.1 mL) and DMF (10 mL) as solvent, product **18b** was obtained (45.5 g, 0.1 mol) as a deep yellow solid in 99% yield.**Mp**: 288-290 ˚C.**IR (NaCl)** ν_{max} : 3172, 1681, 1628, 1225 cm^{-1}. **Analysis**: Calcd. for $C_{22}H_{22}N_2O_6$: C 64.38, H 5.40, N 6.83. Found C 64.25, H 5.40, N 6.78. **^{1}H-RMN** (250MHz, $CDCl_3$) δ: 8.64 (1H, s, N**H**), 6.90-6.84 (3H, m, **H3'**, **H4'**, C**H**-C3), 6.78 (1H, d, *J* = 2.57 Hz, **H6'**), 3.84 (3H, s, C2'-OC**H$_3$**), 3.72 (3H, s, C5'-OC**H$_3$**). **^{13}C- RMN** (63MHz, $CDCl_3$) δ: 157.3 (**C1**), 154.4 (**C5'**), 150.7 (**C2'**), 126.3 (**C3**), 123.4 (**C1'**), 116.9 (**C6'**), 116.2 (**C4'**), 114.0* (C3-**C**H), 113.9* (**C3'**), 57.1 (C2'-O**C**H_3), 55.1 (C5'-O**C**H_3).

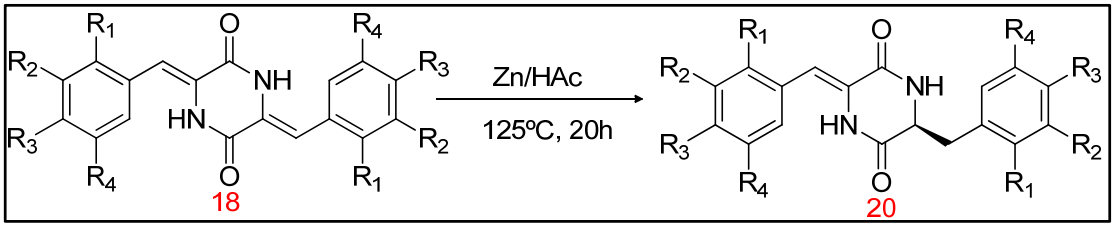
5.3.7. Synthesis of (3*Z*,6*Z*)-3,6-bis(2,4,5-trimethoxy-3-methylbenzylidene)piperazine-2,5-dione 19.



To compound **13** (1.0 g, 5.0 mmol), 3-methyl-2,4,5-trimethoxybenzaldehyde (**17**) (3.0 g, 0.014 mol), as starting material, cesium carbonate (2.04 g, 6.26 mmol) and DMSO (1.4 mL) and AcOEt (5.0 mL) as solvents, were added. The mixture was stirred at 80 ºC for 3 h and then, was cooled at room temperature. After adding $CHCl_3$ (75 mL), the mixture was filtered to remove the cesium salts and the organic layer was evaporated *in vacuo*. To the red-brown solution was then added diethyl ether in order to precipitated compound **19** (2.20 g, 0.0043 mol) as a deep yellow solid in 86% yield; **Mp** 120-121ºC; **IR (NaCl)** ν_{max}

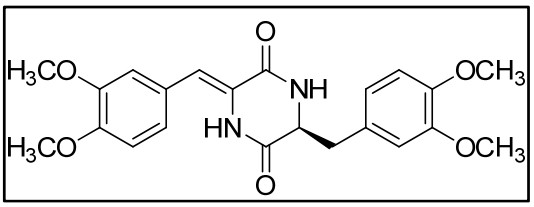
2930, 2300, 1690, 1621 cm^{-1}; **Analysis**: Calcd. for $C_{26}H_{30}N_2$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.58; H, 6.00; N, 5.53; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 9.59 (br. s, 2H, **NH**), 6.88 (s, 2H, **CH**-C3, **CH**-C6), 6.69 (s, 2H, **CH_{Ar}**), 3.84 (s, 6H, 2 x **OCH_3**), 3.83 (s, 6H, 2 x **OCH_3**), 3.66 (s, 6H, 2 x **OCH_3**), 2.26 (s, 6H, 2 x **CH_3**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 157.5 (**C1, C4**), 149.8 (2 x **C**-OCH_3), 149.3 (2 x **C**-OCH_3), 149.2 (2 x **C**-OCH_3), 126.8 (2 x **C**-CH_3), 125.6 (**C3, C6**), 121.7 (**C1'**, **C1''**), 113.9 (**C**H-C3, **CH**-C6), 112.3 (**C6'**, **C6''**), 61.2, 60.6, 56.0 (6 x **OCH_3**), 9.7 (2 x **CH_3**).

5.3.8. General procedure to obtain (*Z*)-dimethoxy-3-benzyl-6-benzylidenepiperazine-2,5-diones 20a–20c.



To compounds **18a–18b** (1.0 eq) in acetic acid (150–350 mL), dust Zn (11.1 eq) was added. The solution was stirred at 125 ºC for 20 h and then, the pale yellow solution was filtered and concentrated under reduced pressure to give a yellow solid, which was washed with saturated aqueous solution of $NaHCO_3$ and extracted with $CHCl_3$ (3 x 50 mL). The solvent was evaporated under reduced pressure to provide compounds **20a–20b** as pale yellow solids.

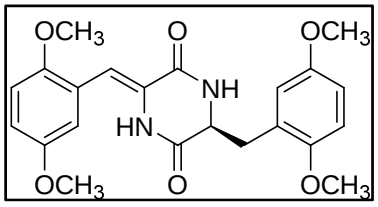
5.3.8.1. Synthesis of (*Z*)-3-(3,4-dimethoxybenzyl)-6-(3,4-dimethoxybenzylidene)piperazine-2,5-dione 20a.



According to the general procedure **4.3.8** using compound **18a** (5.00 g, 0.012 mol) as starting material, powder Zn (17.4 g, 26.6 mmol), and acetic acid (354 mL) as solvent, product **20a** was obtained (4.10 g, 9.60 mmol) as a pale yellow solid in 80% yield; **Mp** 95-96 ºC; **IR (NaCl) ν_{max}** 3200, 2930 cm^{-1}; **Analysis**: Calcd. for $C_{22}H_{24}N_2$: C, 64.07; H, 5.87; N, 6.7. Found: C, 64.00; H, 5.80; N, 6.69; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.92 (s,

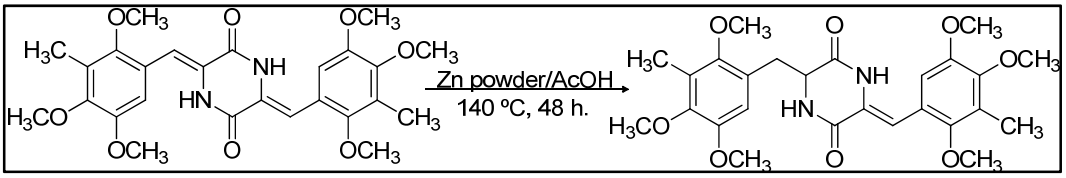
1H, N**H**), 6.85-6.70 (m, 7H, C**H**$_{Ar}$, C**H**-C6), 4.43–4.38 (m, 1H, **H3**), 3.89 (s, 3H, OC**H**$_3$), 3.87 (s, 3H, OC**H**$_3$), 3.84 (s, 3H, OC**H**$_3$), 3.79 (s, 3H, OC**H**$_3$), 3.25 (dd, *J* = 13.8, 3.7 Hz, 1H, C**H**$_2$-C3), 3.06 (dd, *J* = 13.9, 7.3 Hz, 1H, C**H**$_2$-C3), 2.95–2.56 (m, 1H, C**H**-C6); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 165.3, 160.4 (**C1, C4**), 149.6, 149.5, 149.3, 148.7 (4 x **C**-OCH_3), 126.9, 125.4, 124.2 (**C6, C1', C1''**), 122.2, 120.8, 116.5, 112.9, 111.9, 111.7, 111.6 (6 x **C**H$_{Ar}$, **C**H-C6), 57.3 (**C3**), 56.0 (4 x O**C**H$_3$), 40.7 (**C**H$_2$-C3).

5.3.8.2. Synthesis of (Z)-3-(2,5-dimethoxybenzyl)-6-(2,5-dimethoxybenzylidene)piperazine-2,5-dione 20b.



According to the general procedure **4.3.8** using compound **18b** (5.00 g, 0.012 mol) as starting material, powder Zn (8.5 g, 0.130 mol) and acetic acid (177 mL) as solvent, product **20b** was obtained (4.16 g, 9.72 mmol) as a pale yellow solid in 83% yield; **Mp** 160-161 ºC; **IR (NaCl) ν_{max}** 3200, 2900, 1603, 1620 cm^{-1}; **Analysis**: Calcd. for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 64.07; H, 5.73; N, 6.75; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.61 (s, 1H, **NH**), 6.90 (d, *J* = 9.0 Hz, 1H, **H3''**), 6.87 (dd, *J* = 9.0, 2.9 Hz, 1H, **H4''**), 6.82-6.75 (m, 4H, C**H**-C6, **H3', H4', H6'**), 6.73 (d, *J* = 2.8 Hz, 1H, **H6''**), 6.13 (s, 1H, **H2**), 4.47 (ddd, *J* = 8.0, 4.2, 1.7 Hz, 1H, **H3**), 3.86, 3.80, 3.78, 3.70 (4 x s, 4 x 3H, 4 x OC**H**$_3$), 3.50 (dd, *J* = 13.6, 4.2 Hz, 1H, C**H**$_2$-C3), 2.93 (dd, *J* = 13.6, 8.1 Hz, 1H, C**H**$_2$-C3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.4 (**C4**), 160.0 (**C1**), 154.2, 153.8, 152.1, 150.5 (4 x **C**-OCH_3), 125.8 (**C6**), 124.4 (**C1''**), 123.2 (**C1'**), 117.7 (**C6''**), 116.5, 115.6, 113.9, 113.5, 113.1, 111.7 (**C3', C4', C6', C3'', C4'', ó C**H-C6), 57.0, 56.0, 55.9, 55.8 (4 x O**C**H$_3$), 55.7 (**C3**), 35.2 (**C**H$_2$-C3).

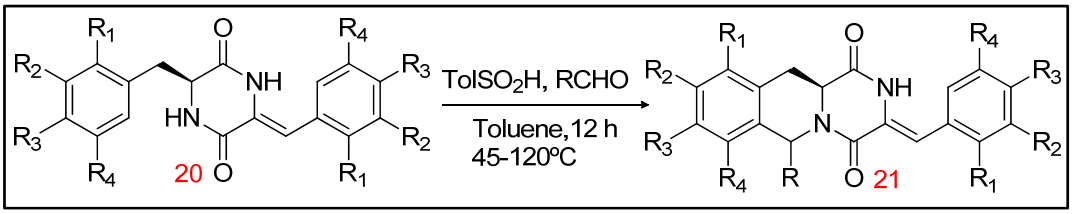
5.3.8.3. Synthesis of (Z)-3-(2,4,5-trimethoxy-3-methylbenzyl)-6-(2,4,5-trimethoxy-3-methylbenzylidene)piperazine-2,5-dione 20c.



To compound **19** (4.00 g, 8.00 mmol) in acetic acid (50 mL), dust Zn (11.1 eq) was added. The reaction mixture was stirred at 140 ºC for 48 h by adding 5.0 eq more of powder Zn

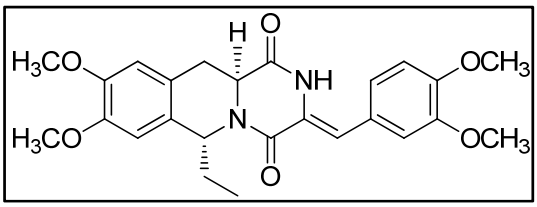
every 12 h. The black solution was filtered and concentrated under reduced pressure to give a yellow solid that was washed with a saturate solution of $NaHCO_3$ and extracted with $CHCl_3$ (3 x 50 mL). The solvent was evaporated *in vacuo* affording compound **20c** (1.55 g, 3.10 mmol) as a brown solid in 39% yield. **Mp**: 142-145 ºC. IR (NaCl) ν_{max} 3230, 1686, 1636, 1229 cm^{-1}. **Analysis**: Calcd. for $C_{26}H_{32}N_2O_8$: C 62.39, H 6.44, N 5.60. Found C 62.45, H 6.52, N 5.59. **^{1}H-RMN** (250 MHz, $CDCl_3$) δ 9.28 (sa, 1 H, **H1**), 6.70 (s, 1H, C**H**-C3), 6.64 (sa, 1H, **H4**), 6.61 (s, 1H, **H6''**), 6.56 (1H, s, **H6''**), 4.49-4.45 (m, 1H, **H6**), 3.85, 3.83, 3.77, 3.72, 3.68 y 3.58 (6 x s, 6 x 3H, 6 x OC**H**$_3$), 3.36 (dd, 1H, *J* = 13.7 y 4.1 Hz, C**H**$_2$-C6), 3.02 (dd, 1H, *J* = 13.7 y 7.7 Hz, C**H**$_2$-C6), 2.23 (s, 3H, C3''-C**H**$_3$), 2.18 (s, 3H, C3'-C**H**$_3$). **^{13}C-RMN** (63 MHz, $CDCl_3$) δ: 165.9 (**C4**), 160.9 (**C1**), 151.6 (**C2''**), 150.0, 149.8, 149.3, 149.1, 147.9 (**C2''**, **C4''**,**C5''**, **C4'**, **C5'**), 126.8* (**C3''**), 126.4 (**C3'**), 125.5 (**C6**), 123.3 (**C1'**), 121.8* (**C1'**), 113.7 (**C**H-C3), 112.3 (**C6''**), 112.0 (**C6'**), 61.4, 61.1, 60.8, 60.6, 60,56 (5 x OC**H**$_3$), 56.9 (**C6**), 56.2 (OC**H**$_3$), 35.3 (C**H**$_2$-C6), 10.1 y 9.9 (C3'-**C**H$_3$, C3''-**C**H$_3$).

5.3.9. General procedure to obtain (*Z*)-3-(dimethoxybenzylidene)dimethoxy-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones 21a–20r.



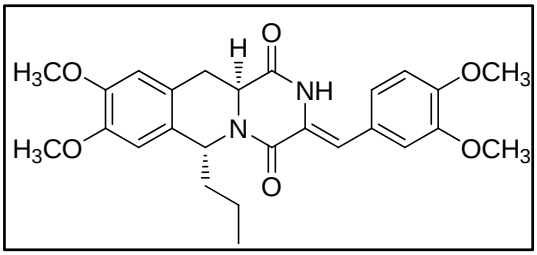
To a solution of **20** (1.00 eq) in toluene (0.5 – 2.0 mL), *p*-toluene sulfinic acid (0.96–4.00 eq) and alkyl or aryl aldehyde (1.3–29.9 eq) were added. The reaction mixture was stirred at 45-140 ºC for 12 h. Then, was quenched with saturated aqueous solution of $NaHCO_3$, extracted with DCM (2 x 20 mL), dried over anhydrous Na_2SO_4 and filtered. The solution was concentrated *in vacuo* and purified by flash column chromatography using petroleum ether:diethyl ether as eluent to provide compounds **21a – 21p**.

5.3.9.1. Synthesis of (*Z*)-3-(3,4-dimethoxybenzyl)-6-ethyl-8,9-dimethoxy-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 21a.



Obtained according to the general procedure **4.3.9** using compound **20a** (0.10 g, 0.23 mmol) as starting material, *p*-toluene sulfinic acid (0.049 g, 0.32 mmol), 1-propionaldehyde (0.40 g, 6.89 mmol) and toluene (2.0 mL) as solvent at 45 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **21a** (0.11 g, 0.23 mmol) as an orange solid in 99% yield; **Mp** 192–193 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1700, 1655 cm^{-1}; **Analysis**: Calcd. for $C_{25}H_{30}N_2O_6$: C, 66.06; H, 6.65; N, 6.16. Found: C, 66.00; H, 6.60; N, 6.19; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.10 (s, 1H, N**H**), 7.01 (s, 1H, C**H**-C3), 6.96 (dd, *J* = 8.3, 1.8 Hz, 1H, **H6''**), 6.90 (d, *J* = 8.3 Hz, 1H, **H5''**), 6.82 (d, *J* = 1.7 Hz, 1H, **H2''**), 6.64* (s, 1H, **H7**), 6.56* (s, 1H, **H10**), 5.74 (dd, *J* = 10.4, 4.4 Hz, 1H, **H6**), 4.50 (dd, *J* = 12.1, 4.4 Hz, 1H, **H11a**), 3.90 (s, 3H, OC**H$_3$**), 3.88 (s, 3H, OC**H$_3$**), 3.86 (s, 3H, OC**H$_3$**), 3.84 (s, 3H, OC**H$_3$**), 3.27 (dd, *J* = 16.0, 4.4 Hz, 1H, **H11**), 3.05 (dd, *J* = 15.9, 12.2 Hz, 1H, **H11**), 1.96–1.79 (m, 2H, **H1'**), 1.02 (t, *J* = 7.4 Hz, 3H, **H2'**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 165.2, 157.3 (**C1, C4**), 149.7, 149.4, 148.2, 148.1 (4 x **C**-OCH$_3$), 128.4, 125.9, 124.4, 123.0 (**C1'', C3, C6a, C10a**), 120.6, 116.8, 111.9, 111.7, 111.1, 109.8 (**C**H$_{Ar}$, **C**H-C3), 56.1, 56.0 (4 x O**C**H$_3$), 54.0 (**C11a**), 52.8 (**C6**), 34.2 (**C11**), 29.4 (**C1'**), 11.1 (**C2'**).

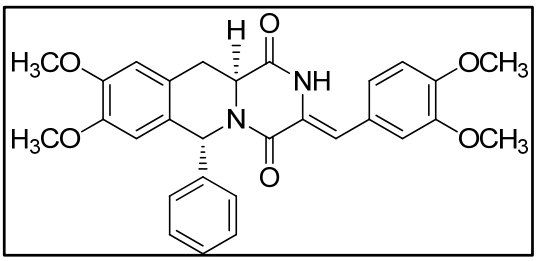
5.3.9.2. Synthesis of (*Z*)-3-(3,4-dimethoxybenzyl)-8,9-dimethoxy-6-propyl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-b]isoquinoline-1,4-dione 21b.



Obtained according to the general procedure **4.3.9** using compound **20a** (0.20 g, 0.47 mmol), and 1-butyraldehyde (0.2 g, 2.77 mmol) as starting materials, *p*-toluene sulfinic acid (0.098 g, 0.63 mmol), and toluene (2.0 mL) as solvent at 45 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **21b** (0.055 g, 0.39 mmol) as an orange solid in 84% yield; **Mp** 115–116 ºC; **IR (NaCl) ν_{max}** 3210, 2910, 1663, 1605 cm^{-1}; **Analysis:** Calcd. for $C_{26}H_{32}N_2O_6$: C, 66.65; H,

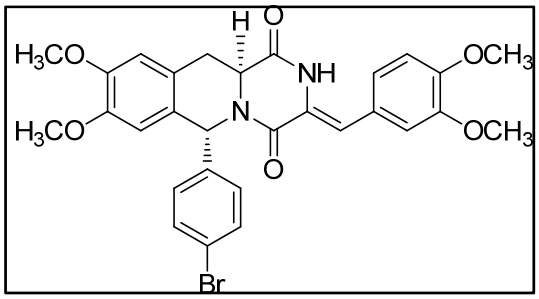
6.88; N, 5.98. Found: C, 66.50; H, 6.80; N, 5.99; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.04 (s, 1H, N**H**), 7.02 (s, 1H, C**H**-C3), 6.97 (dd, *J* = 8.4, 1.4 Hz, 1H, **H6''**), 6.91 (d, *J* = 8.3 Hz, 1H, **H5''**), 6.82 (d, *J* = 1.2 Hz, 1H, **H2''**), 6.63* (s, 1H, **H7**), 6.57* (s, 1H, **H10**), 5.82 (t, *J* = 7.4 Hz ,1H, **H6**), 4.52 (dd, *J* = 12.1, 4.4 Hz, 1H, **H11a**), 3.91 (s, 3H, OC**H$_3$**), 3.89 (s, 3H, OC**H$_3$**), 3.88 (s, 3H, OC**H$_3$**), 3.85 (s, 3H, OC**H$_3$**), 3.28 (dd, *J* = 16.0, 4.3 Hz, 1H, **H11**), 3.06 (dd, *J* = 15.8, 12.2 Hz, 1H, **H11**), 1.84 (dd, *J* = 15.2, 7.7 Hz, 2H, **H1'**), 1.67 – 1.35 (m, 2H, **H2'**), 0.99 (t, *J* = 7.3 Hz, 3H, **H3'**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 165.2 (**C1**), 157.2 (**C4**), 149.8, 149.5, 148.3, 148.1 (4 x **C**-OCH$_3$), 128.6, 125.9, 124.4, 122.9 (**C10a, C6a, C1'', C**H-C3), 120.6* (**C2''**), 116.8 (**C**H-C3), 111.9* (**C5''**), 111.7, 111.1 (**C7, C10**), 109.8* (**C6''**), 56.1, 56.1 (4 x OCH$_3$), 52.8, 52.6 (**C6, C11a**), 38.7 (**C11**), 34.2 (**C1'**), 19.8 (**C2'**), 14.1 (**C3'**).

5.3.9.3. Synthesis of (*Z*)-3-(3,4-dimethoxybenzylidene)-8,9-dimethoxy-6-phenyl-2,3,11,11a-tetrahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4(6*H*)-dione 21c.



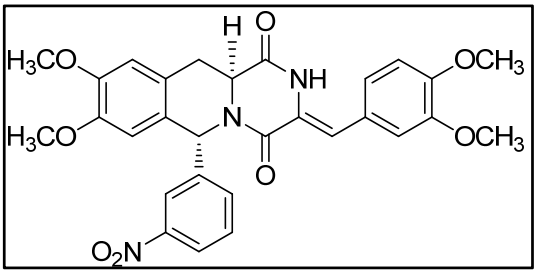
Obtained according to the general procedure **4.3.9** using compound **20a** (0.1 g, 0.23 mmol), and benzaldehyde (0.052 g, 0.49 mmol) as starting materials, *p*-toluene sulfinic acid (0.13 g, 0.83 mmol) and toluene (0.50 mL) as solvent at 90 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **21c** (0.11 g, 0.21 mmol) as a yellow solid in 74 % yield; **Mp** 119 – 120 ºC; **IR (NaCl) ν$_{max}$** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis:** Calcd. for $C_{29}H_{28}N_2O_6$: C, 69.59; H, 5.64; N, 5.60. Found: C, 69.50; H, 5.70; N, 5.59; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.96 (s, 1H, N**H**), 7.28 – 7.22 (m, 5H, C**H$_{Ar}$'**), 7.05 (s, 1H, C**H**-C3), 7.02 (s, 1H, **H6**), 6.90 (dd, *J* = 8.5, 1.5 Hz, 1H, **H6''**), 6.85 (d, *J* = 8.3 Hz, 1H, **H5''**), 6.77 (d, *J* = 1.5 Hz, 1H, **H2''**), 6.64* (s, 1H, **H7**), 6.47* (s, 1H, **H10**), 4.37 (dd, *J* = 12.2, 4.5 Hz, 1H, **H11a**), 3.86 (s, 6H, OC**H$_3$**), 3.84 (s, 3H, OC**H$_3$**), 3.71 (s, 3H, OC**H$_3$**), 3.33 (dd, *J* = 16.2, 4.5 Hz, 1H, **H11**), 3.10 (dd, *J* = 16.0, 12.3 Hz, 1H, **H11**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 165.0 (**C1**), 156.6 (**C4**), 149.8, 149.5, 148.6, 148.3 (4 x **C**-OCH$_3$), 141.1 (**C1'**), 129.1, 128.8 (**C2', C3', C6', C5'**), 128.4 (**C4'**), 125.8, 125.1, 124.5, 124.4 (**C6a, C10a, C3, C1''**), 120.6 (**C2''**), 116.8 (**C**H-C3), 111.8, 111.7 (**C7, C10**), 110.8 (**C5'', C6''**), 56.1 (4 x OCH$_3$), 55.4 (**C6**), 52.4 (**C11a**), 34.0 (**C11**).

5.3.9.4. Synthesis of (*Z*)-6-(4-bromophenyl)-3-(3,4-dimethoxybenzyl)-8,9-dimethoxy-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 21d.



Obtained according to the general procedure **4.3.9** using compound **20a** (0.1 g, 0.23 mmol), and 4-bromobenzaldehyde (0.2 g, 2.77 mmol) as starting materials, *p*-toluene sulfinic acid (0.12 g, 0.76 mmol) and toluene (0.50 mL) as solvent at 110 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **21d** (0.15 g, 0.25 mmol) as a brown solid in 53% yield; **Mp** 92 – 94 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis:** Calcd. for $C_{29}H_{29}N_2O_6$: C, 59.90; H, 5.03; N, 4.82. Found: C, 59.76; H, 5.06; N, 4.89; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.98 (s, 1H, N**H**), 7.32 – 7.27 (m, 4H, **H2', H3', H5', H6'**), 7.09 (s, 1H, C**H**-C3), 7.06 (s, 1H, **H6**), 6.92 (dd, *J* = 8.4, 1.4 Hz, 1H, **H6''**), 6.91 (d, *J* = 8.2 Hz, 1H, **H5''**), 6.81 (d, *J* = 1.4 Hz, 1H, **H2''**), 6.68 (s, 1H, **H10**), 6.51 (s, 1H, **H7**), 4.41 (dd, *J* = 12.2, 4.4 Hz, 1H, **H11a**), 3.90 (s, 6H, O**CH$_3$**), 3.88 (s, 6H, O**CH$_3$**), 3.76 (s, 3H, O**CH$_3$**), 3.37 (dd, *J* = 16.1, 4.4 Hz, 1H, **H11**), 3.14 (dd, *J* = 16.0, 12.3 Hz, 1H, **H11**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.8 (**C1**), 156.7 (**C4**), 149.8, 149.6, 148.8, 148.5 (4 x **C**-OCH_3), 140.2 (**C1'**), 131.9 (**C3', C5'**), 130.8 (**C2', C6'**), 125.7, 124.5, 124.3, 122.6 (**C6a, C10a, C4', C3, C1''**), 120.7* (**C2''**), 117.1 (**C**H-C3), 111.9*, 111.8* (**C5'', C6''**), 110.9 (**C10**), 110.6 (**C7**), 56.1 (4 x O**C**H$_3$), 54.9 (**C6**), 52.4 (**C11a**), 33.9 (**C11**).

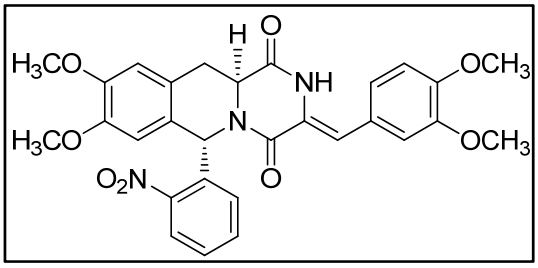
5.3.9.5. Synthesis of (*Z*)-3-(3,4-dimethoxybenzylidene)-8,9-dimethoxy-6-(3-nitrophenyl)-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 21e.



Obtained according to the general procedure **4.3.9** using compound **20a** (0.2 g, 0.47 mmol) and 3-nitrobenzaldehyde (0.14 g, 0.94 mmol) as starting materials, *p*-toluene sulfinic acid (0.070 g, 0.45 mmol) and toluene (1.0 mL) as solvent at 100 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded

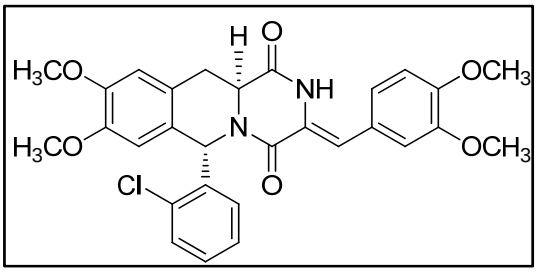
product **21e** (0.14 g, 0.25 mmol) as an orange solid in 53% yield as a rotamers mixture; **Mp** 217 – 218 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1700, 1650 cm^{-1}; **Analysis:** Calcd. for $C_{29}H_{27}N_3O_8$: C, 63.85; H, 4.99; N, 7.70. Found: C, 64.00; H, 5.80; N, 7.59; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.16 (ddd, *J* = 8.1, 2.2, 1.0 Hz, 1H, **H6'**), 8.11 – 8.08 (m, 2H, N**H, H2'**), 7.67 (d, *J* = 7.8 Hz, 1H, **H4'**), 7.51 (t, *J* = 7.9 Hz, 1H, **H5'**), 7.13 (s, 1H, **H6**), 7.06 (s, 1H, C**H**-C3), 6.94 (dd, *J* = 8.6, 1.7 Hz, 1H, **H6''**), 6.88 (d, *J* = 8.4 Hz, 1H, **H5''**), 6.81 (d, *J* = 1.6 Hz, 1H, **H2''**), 6.70 (s, 1H, **H10**), 6.44 (s, 1H, **H7**), 4.32 (dd, *J* = 12.2, 4.4 Hz, 1H, **H11a**), 3.91 (s, 3H, OC**H$_3$**), 3.88 (s, 3H, OC**H$_3$**), 3.86 (s, 3H, OC**H$_3$**), 3.74 (s, 3H, OC**H$_3$**), 3.39 (dd, *J* = 16.2, 4.3 Hz, 1H, **H11**), 3.16 (dd, *J* = 16.0, 12.3 Hz, 1H, **H11**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.4 (**C1**), 156.9 (**C4**), 149.7, 149.6, 149.1, 148.7 (4 x **C**-OCH_3), 143.2 (**C1'**), 135.1 (**C4'**), 129.8 (**C5'**), 125.6, 124.6, 124.0, 123.8, 123.5 (**C2', C6'**), 120.7 (**C6''**), 117.5 (**C**H-C3), 111.9, 111.7 (**C2'', C5''**), 111.2 (**C10**), 110.4 (**C7**), 56.1 (4 x O**C**H_3), 54.7 (**C6**), 52.6 (**C11a**), 33.8 (**C11**).

5.3.9.6. Synthesis of (*Z*)-3-(3,4-dimethoxybenzyl)-8,9-dimethoxy-6-(2-nitrophenyl)-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 21f.



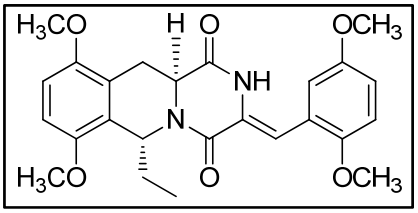
Obtained according to the general procedure **4.3.9** using compound **20a** (0.10 g, 0.23 mmol) and 2-nitrobenzaldehyde (0.046 g, 0.30 mmol) as starting materials, *p*-toluene sulfinic acid (0.049 g, 0.32 mmol), and toluene (2.0 mL) as solvent at 110 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether: diethyl ether as eluent afforded product **21f** (0.052 g, 0.093 mmol) as an orange solid in 40% yield; **Mp** 184–185 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis:** Calcd. for $C_{29}H_{29}N_3O_8$: C, 63.61; H, 5.34; N, 7.67. Found: C, 63.50; H, 5.20; N, 7.59; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.11* (s, 1H, **H3'**), 8.06* (s, 1H, **H4'**), 7.68 (d, *J* = 7.6 Hz, 1H, **H6'**), 7.42 (t, *J* = 7.5 Hz, 1H, **H5'**), 7.15 (s, 1H, **H6**), 7.08 (s, 1H, C**H**-C3), 6.93* (s, 1H, **H2''**), 6.91 (s, 1H, **H10**), 6.82 (s, 1H, **H5''**), 6.71* (s, 1H, **H6''**), 6.45 (s, 1H, **H7**), 4.33 (dd, *J* = 12.1, 4.1 Hz, 1H, **H11a**), 3.91 (s, 3H, OC**H$_3$**), 3.90 (s, 3H, OC**H$_3$**), 3.88 (s, 3H, OC**H$_3$**), 3.75 (s, 3H, OC**H$_3$**), 3.41 (dd, *J* = 16.2, 4.1 Hz, 1H, **H11**), 3.17 (dd, *J* = 15.8, 12.4 Hz, 1H, **H11**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.5 (**C1**), 156.9 (**C4**), 149.8, 149.6, 149.1, 148.7 (4 x **C**-OCH_3), 143.2 (**C1'**), 135.2 (**C6'**), 129.9 (**C5'**), 125.8*, 125.6*, 124.7*, 124.0* (**C6a, C10a, C3, C1''**), 123.9, 123.6 (**C4', C3'**), 123.5* (**C2'**), 120.7** (**H2''**), 117.5 (CH-C3), 111.9, 111.8 (**H5'', H10**), 111.2** (**H6''**), 110.5 (**H7**), 56.1 (4 x O**C**H_3), 54.7 (**C6**), 52.7 (**C11a**), 30.4 (**C11**).

5.3.9.7. Synthesis of (*Z*)-6-(2-chlorophenyl)-3-(3,4-dimethoxybenzylidene)-8,9-dimethoxy-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 21g.



Obtained according to the general procedure **4.3.9** using compound **20a** (0.2 g, 0.47 mmol) and 2-chlorobenzaldehyde (0.37 g, 2.63 mmol) as starting materials, *p*-toluene sulfinic acid (0.070 g, 0.45 mmol) and toluene (0.50 mL) as solvent at 100 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **21g** (0.12 g, 0.22 mmol) as a brown solid in 47% yield; **Mp** 104 – 106 ºC; **IR (NaCl) ν_{max}** 3190, 2930, 1673, 1615 cm^{-1}; **Analysis:** Calcd. for $C_{29}H_{27}N_2$: C, 65.11; H, 5.09; N, 5.24 Found: C, 65.00; H, 5.08; N, 5.19; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.99 (s, 1H, N**H**), 7.44* (dd, *J* = 7.9, 1.2 Hz, 1H, **H2'**), 7.25** (td, *J* = 7.6, 1.6 Hz, 1H, **H3'**), 7.19 (s, 1H, C**H**-C3), 7.14** (td, *J* = 7.6, 1.3 Hz, 1H, **H4'**), 7.06 (s, 1H, **H6**), 6.94 (dd, *J* = 8.5, 1.6 Hz, 1H, **H6''**), 6.87 (d, *J* = 8.3 Hz, 1H, **H5''**), 6.79* (dd, *J* = 9.0, 1.5 Hz, 2H, **H6', H2''**), 6.65, 6.50 (2s, 2 x 1H, **H7, H10**), 4.36 (dd, *J* = 12.2, 4.8 Hz, 1H, **H11a**), 3.88 (s, 3H, OC**H$_3$**), 3.87 (s, 3H, OC**H$_3$**), 3.86 (s, 3H, OC**H$_3$**), 3.75 (s, 3H, OC**H$_3$**), 3.31 (dd, *J* = 16.2, 4.8 Hz, 1H, **H11**), 3.13 (dd, *J* = 16.1, 12.3 Hz, 1H, **H11**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 165.4 (**C1**), 157.4 (**C4**), 149.8, 149.5, 148.9, 148.5 (4 x **C**-OCH_3), 137.6 (**C1'**), 134.9 (**C2'**), 131.9, 130.5, 129.8, 126.8 (**C3', C4', C5', C6'**), 125.9, 125.4, 124.5, 124.3 (**C6a, C10a, C3, C1''**), 120.7* (**C2''**), 117.5 (**C**H-C3), 112.0, 111.7 (**C7, C10**), 111.1*, 110.7* (**C5'', C6''**), 56.1 (4 x OCH_3), 53.6 (**C6**), 53.1 (**C11a**), 33.8 (**C11**).

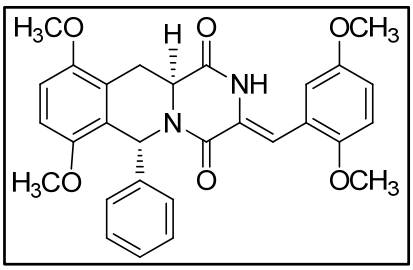
5.3.9.8. Synthesis of (*Z*)-3-(2,5-dimethoxybenzylidene)-6-ethyl-7,10-dimethoxy-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 21h.



Obtained according to the general procedure **4.3.9** using compound **20b** (0.1 g, 0.23 mmol) and 1-propionaldehyde (0.400 g, 6.89 mmol) as starting materials, *p*-toluene sulfinic acid (0.049 g, 0.39 mmol) and toluene (1.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **21h** (0.030 g, 0.064 mmol) as a brown solid in 27% yield; **Mp** 84 – 85 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1};

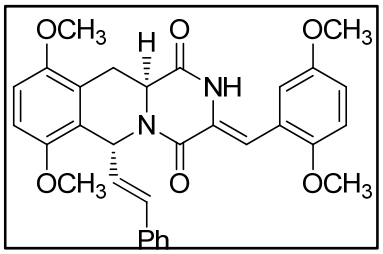
Analysis: Calcd. for $C_{25}H_{28}N_2O_6$: C, 66.36; H, 6.24; N, 6.19. Found: C, 66.20; H, 6.43; N, 6.20; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.73 (s, 1H, N**H**), 6.97-6.66 (m, 6H, **H8, H9**, **CH**-C3, 3 x C**H**-Ar), 5.94 (dd, *J* = 11.1, 3.3 Hz, 1H, **H6**), 4.49 (dd, *J* = 12.4, 4.8 Hz, 1H, **H11a**), 3.88 (s, 3H, OC**H$_3$**), 3.82 (s, 3H, OC**H$_3$**), 3.77 (s, 3H, OC**H$_3$**), 3.75 (s, 3H, OC**H$_3$**), 3.44 (dd, *J* = 17.4, 4.9 Hz, 1H, **H11**), 2.75 (dd, *J* = 17.4, 12.4 Hz, 1H, **H11**), 2.18 – 2.12 (m, 1H, C**H$_2$**-C6), 1.62 – 1.53 (m, 1H, C**H$_2$**-C6), 1.02 (t, *J* = 7.4 Hz, 3H, C**H$_3$**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 165.5, 157.6 (**C1, C4**), 154.2, 151.0, 150.3, 150.0 (4 x **C**-OCH_3), 127.0, 125.8, 123.3, 121.6 (**C3, C6a, C10a, C**-Ar), 116.5, 115.5, 113.8, 113.74, 108.4, 108.2 (**C8, C9, C3**, 3 x **C**H-Ar), 57.0, 55.9, 55.8, 55.7 (4 x OCH_3), 51.7 (**C11a**), 50.6 (**C6**), 29.4 (**C11**), 26.0 (CH_2-C6), 11.1 (**C**H_3).

5.3.9.9. Synthesis of (*Z*)-3-(2,5-dimethoxybenzylidene)-7,10-dimethoxy-6-phenyl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 21i.



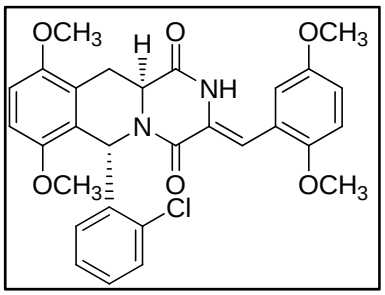
Obtained according to the general procedure **4.3.9** using compound **20b** (0.1 g, 0.23 mmol) and 1-benzaldehyde (0.048 g, 0.45 mmol) as starting materials, *p*-toluene sulfinic acid (0.049 g, 0.39 mmol) and toluene (2.0 mL) as solvent to 120 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **21i** (0.054 g, 0.094 mmol) as a yellow solid in 41% yield; **Mp** 90 – 91 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{29}H_{28}N_2O_6$: C, 69.59; H, 5.64; N, 5.60. Found: C, 69.44; H, 5.43; N, 5.50; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.61 (s, 1H, N**H**), 7.25 – 6.65 (m, 12H, **H6, H8, H9**, **H2'- H6'**, C**H**-C3, 3 x C**H**-Ar), 4.30 (dd, *J* = 12.4, 4.7 Hz, 1H, **H11a**), 3.86 (s, 3H, OC**H$_3$**), 3.81 (s, 3H, OC**H$_3$**), 3.77 (s, 3H, OC**H$_3$**), 3.61(s, 3H, OC**H$_3$**), 3.76 (s, 3H, OC**H$_3$**), 3.50 (dd, *J* = 17.5, 4.8 Hz, 1H, **H11**), 2.85 (dd, *J* = 17.1, 12.5 Hz, 1H, **H11**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 165.2, 156.8 (**C1, C4**), 154.2, 151.1, 150.5, 150.3 (O**CH$_3$**), 140.4 (**C1**), 128.5** (**C2'', C6''**), 128.4* (**C8**) 128.4** (**C3'', C5''**), 127.9* (**C9**), 125.8, 123.8, 123.4, 122.9 (**C3, C6a, C10a**, **C**-Ar), 116.4*, 115.5*, 113.8*, 108.9*, 108.7* (**C4'**, **C**H-C3, 3 x **C**H-Ar), 56.9, 56.0, 55.9, 55.8 (OCH_3), 51.8, 51.7 (**C6, C11a**), 29.3 (**C11**).

5.3.9.10. Synthesis of (*Z*)-3-(2,5-dimethoxybenzylidene)-7,10-dimethoxy-6-((*E*)-styryl)-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 21j.



Obtained according to the general procedure **4.3.9** using compound **20b** (1.0 g, 2.3 mmol), cinnamaldehyde (0.37 g, 2.8 mmol) as starting material, *p*-toluene sulfinic acid (0.55 g, 3.5 mmol) and Toluene (12.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether: diethyl ether as eluent afforded product **21j** (0.512 g, 0.97 mmol) as a yellow solid in 42% yield. as a mixture of amide rotamers in $CDCl_3$, 25 ºC; **Mp** 108 – 109 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{31}H_{30}N_2O_6$: C, 70.71; H, 5.74; N, 5.32. Found: C, 70.54; H, 5.79; N, 5.50; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.78 (s, 1H, N**H**), 7.36 – 6.63 (m, 14H, **H8, H9, H6, H1', H2', H2'',H3'',H4'',H5'',H6''**,C**H**-C3, 3xC**H**-Ar), 4.59 (m, 1H, **H11a**), 3.99 – 3.68 (m, 12H, OC**H$_3$**), 3.59-3.46 (m, 1H, **H11**), 3.14 – 2.57 (m, 3H, **H11**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 165.2, 164.6, 164.1, 157.7, 156.8 (**C1, C4**), 154.1, 151.0, 150.9, 150.4, 150.3, 150.3, 149.9, 149.4 (**C**-OCH$_3$), 136.4, 136.3, 133.0, 132.6 (**CH$_{Ar}$, C4''**), 128.5*, 128.4* (**C2'',C3''**), 127.8, 126.8 (**C1', C2'**), 126.7*, 126.6* (**C6'',C5''**), 125.7, 125.5, 123.8, 123.5, 123.2, 122.9, 122.7, 122.5, 116.4, 115.4, 113.6, 113.0, 108.8, 108.7, 108.5, 108.4 (**CH$_{Ar}$, CH**-C3**, C8, C9**), 56.8, 56.0, 55.8, 55.8, 55.8, 55.6, 55.6 (O**C**H$_3$), 52.0, 51.4, 50.1, 49.4 (**C6, C11a**), 29.3, 29.2 (**C11**).

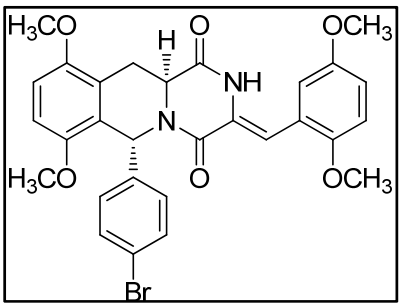
5.3.9.11. Synthesis of (*Z*)-6-(2-chlorophenyl)-3-(2,5-dimethoxybenzylidene)-7,10-dimethoxy-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 21k.



Obtained according to the general procedure **4.3.9** using compound **20b** (0.1 g, 0.23 mmol), and 2-chlorobenzaldehyde (0.15 g, 1.1 mmol) as starting materials, *p*-toluene sulfinic acid (0.049 g, 0.39 mmol), and toluene (2.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **21k** (0.064 g, 0.12 mmol) as a yellow solid in 50% yield as a mixture of amide rotamers in $CDCl_3$, 25 ºC; **Mp** 108 – 109 ºC; **IR(NaCl) ν_{max}** 3190, 2920, 1653, 1620 cm^{-1}; **Analysis:** Calcd. for $C_{29}H_{27}ClN_2O_6$: C, 65.11; H, 5.09; N, 5.24. Found: C, 65.29; H, 5.19; N, 5.05; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.93, 8.68 (N**H**), 7.44

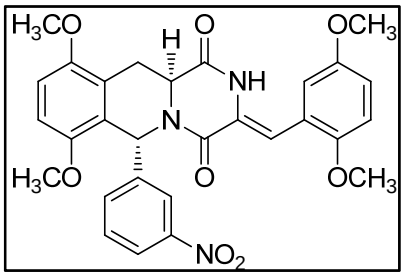
(dd, *J* = 7.8, 1.0 Hz, 1H, C_6-C**H**-Ar), 7.40 (s, 1H, **H6**), 7.22-6.66 (m, 10H, C_6-C**H**-Ar, **H8, H9**, C**H**-C3, C**H**-Ar), 4.32 – 4.18 (m, 1H, **H11a**), 3.96 – 3.59 (m, 12H, OC**H$_3$**), 3.39 (dd, *J* = 17.5, 5.1 Hz, 1H, **H11**), 2.84 (dd, *J* = 17.6, 12.6 Hz, 1H, **H11**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 165.7, 157.6, 157.1 (**C**O), 154.2, 154.1, 151.1, 150.5, 150.3, 150.3 (4 x **C**-OCH$_3$), 136.8, 134.9 (**C**-Ar, **C3**, **C**-C6, **C**-Cl, **C6a, C10a**), 130.7, 130.4, 129.4 (9 x **C**H-**Ar**, **C**H-C3), 129.2, 128.3 (**C**-Ar, **C3**, **C**-C6, **C**-Cl, **C6a, C10a**), 126.4 (9 x **C**H-Ar, **C**H-C3), 126.1, 125.6, 125.4, 124.0, 123.5, 123.1, 123.0 (**C**-Ar, **C3**, **C**-C6, **C**-Cl, **C6a, C10a**), 116.7, 116.5, 115.9, 115.6, 114.6, 113.9, 113.7, 113.7, 109.2, 108.8 (9 x **C**H-Ar, **C**H-C3), 57.0, 56.9, 56.01, 55.9, 55.8, 55.7 (4 x O**C**H$_3$), 52.2 (**C11a**), 49.9 (**C6**), 29.8, 29.2, (**C11**).

5.3.9.12. Synthesis of (*Z*)-6-(4-bromophenyl)-3-(2,5-dimethoxybenzylidene)-7,10-dimethoxy-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 21m.



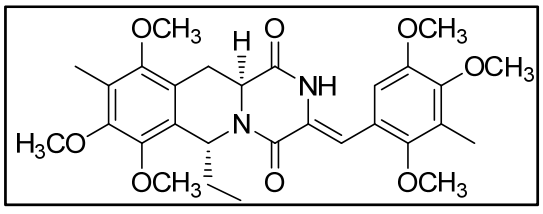
Obtained according to the general procedure **4.3.9** using compound **20b** (0.1 g, 0.23 mmol) 4-bromobenzaldehyde (0.087 g, 0.47 mmol) as starting materials, *p*-toluene sulfinic acid (0.049 g, 0.39 mmol), and toluene (2.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **21m** (0.071 g, 0.12 mmol) as a yellow solid in 41% yield; **Mp** 104 – 105 ºC; **IR (NaCl) ν_{max}** 3180, 2910, 1643, 1610 cm^{-1}; **Analysis:** Calcd. for $C_{29}H_{27}BrN_2O_6$: C, 60.11; H, 4.70; N, 4.83. Found: C, 60.29; H, 4.72; N, 4.80; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.66 (s, 1H, N**H**), 7.39 (d, *J* = 8.5 Hz, 2H, **H3'', H5**''), 7.19 (s, 1H, **H6**), 7.09 (d, *J* = 8.4 Hz, 2H, **H2'', H6''**), 7.02 (s, 1H, C**H**-C3), 6.90 – 6.83 (m, 4H, C**H**-Ar), 4.23 (dd, *J* = 12.4, 4.7 Hz, 1H, **H11a**), 3.86 (s, 3H, OC**H$_3$**), 3.80 (s, 3H, OC**H$_3$**), 3.76 (s, 3H, OC**H$_3$**), 3.61 (s, 3H, OC**H$_3$**), 3.50 (dd, *J* = 17.4, 4.8 Hz, 1H, **H11**), 2.84 (dd, *J* = 17.5, 12.5 Hz, 1H, **H11**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.9 (**C1**), 156.8 (**C4**), 154.2, 151.1, 150.3, 150.3 (4 x **C**-OCH$_3$), 139.60 (**C1''**), 131.6 (**C3'', C5''**), 130.1 (**C2'',C6''**), 125.6, 123.2, 123.1, 122.9 (**C6a, C10a, C3, C1'**), 121.9 (**C**-Br), 116.4*, 115.6* (**C3', C4'**), 113.9 (**C6'**), 113.7 (CH-C3), 109.0*, 108.7* (**C3', C4'**), 56.9, 55.9, 55.7 (4 x OCH$_3$), 51.7 (**C11a**), 51.3 (**C6**), 29.2 (**C11**).

5.3.9.13. Synthesis of (*Z*)-3-(2,5-dimethoxybenzyl)-7,10-dimethoxy-6-(3-nitrophenyl)-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 21n.



Obtained according to the general procedure **4.3.9** using compound **20b** (0.1 g, 0.23 mmol) and 3-nitrobenzaldehyde (0.071 g, 0.47 mmol) as starting materials, *p*-toluene sulfinic acid (0.049 g, 0.39 mmol), and toluene (1.0 mL) as solvent at 120 ºC. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **21n** (0.076 g, 0.135 mmol) as a yellow solid in 58% yield; **Mp** 102 – 103 ºC; **IR (NaCl)** ν_{max} 3180, 2910, 1689, 1627 cm^{-1}; **Analysis:** Calcd. for $C_{29}H_{29}N_3O_8$: C, 63.61; H, 5.34; N, 7.67. Found: C, 63.70; H, 5.56; N, 7.62; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.71 (s, 1H, N**H**), 8.18 – 7.96 (m, 2H, **H5'', H6''**), 7.68 – 7.44 (m, 2H, **H2'', H4''**), 7.29 (s, 1H, **H6**), 7.04 (s, 1H, C**H**-C3), 6.92-6.70 (m, 5H, C**H**-Ar), 4.18 (dd, *J*= 12.4, 4.7 Hz, 1H, **H11a**), 3.87 (s, 3H, OC**H$_3$**), 3.83 (s, 3H, OC**H$_3$**), 3.77 (s, 3H, OC**H$_3$**), 3.61(s, 3H, OC**H$_3$**), 3.53 (dd, *J* = 17.7, 4.6 Hz, 1H, **H11**), 2.86 (dd, *J* = 17.5, 12.5 Hz, 1H, **H11**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.9 (**C1**), 157.4 (**C4**), 154.5, 151.5, 150.6, 150.4 (4 x **C**-OCH_3), 148.8 (**C**-CNO_2), 143.0 (**C**-C6), 134.9* (**C6''**), 129.8* (**C4''**), 125.6, 123.4 (**C3**, **C**-Ar), 123.4*, 123.3* (**C5'', C2''**), 123.3 (**C6a**), 122.4 (**C10a**), 116.8 (**C**H-Ar), 116.0 (**C6'**), 114.7 (**C**H-C3), 114.0 (**C**H-Ar), 109.8, 109.1 (3 x **C**H-**Ar**), 57.2, 56.2, 56.1, 56.0 (4 x OCH_3), 52.3 (**C11a**), 51.6 (**C6**), 29.4 (**C11**).

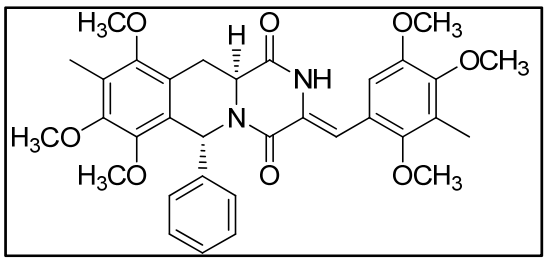
5.3.9.14. Synthesis of (*Z*)-6-ethyl-7,8,10-trimethoxy-9-methyl-3-(2,4,5-trimethoxy-3-methylbenzylidene)-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 21o.



Obtained according to the general procedure **4.3.9** using compound **20c** (0.1 g, 0.19 mmol) and 1-propionaldehyde (0.04 g, 0.69 mmol) as starting materials, *p*-toluene sulfinic acid (0.050 g, 0.32 mmol), and toluene (1.0 mL) as solvent at 140 ºC for 24 h. Purification by flash column chromatography on silica gel using 8:2 petroleum ether:diethyl ether as eluent afforded product **21o** (0.021 g, 0.038 mmol) as a brown solid in 20% yield.; **Mp** 70–72ºC; **IR (NaCl)** ν_{max} 2934, 2350, 1695 cm^{-1}; **Analysis**: Calcd. for $C_{29}H_{36}N_2$: C, 64.43; H, 6.71; N, 5.18. Found: C, 64.49; H, 6.65; N, 5.10; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 9.44 (s, 1H, N**H**), 6.93 (s, 1H, C**H**-C3), 6.63 (s, 1H, C**H**-Ar),

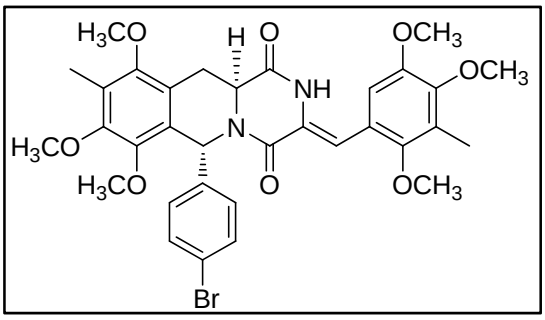
5.88 (dd, *J* = 10.8, 2.6 Hz, 1H, **H6**), 4.47 (dd, *J* = 12.2, 4.6 Hz, 1H, **H11a**), 3.91 (s, 3H, OC**H**$_3$), 3.82 (s, 3H, OC**H**$_3$), 3.80 (s, 6H, 2 x OC**H**$_3$), 3.64 (s, 3H, OC**H**$_3$), 3.63 (s, 3H, OC**H**$_3$), 3.42 (dd, *J* = 17.0, 4.6 Hz, 1H, **H11**), 2.78 (dd, *J* = 16.8, 12.5 Hz, 1H, **H11**), 2.24 (s, 3H, C**H**$_3$-CAr), 2.16 (s, 3H, C**H**$_3$-CAr), 1.44 – 1.27 (m, 1H, **H1'**), 1.03 (t, *J* = 7.4 Hz, 3H, **H2'**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 165.5 (**C1**), 158.1 (**C2**), 152.2, 150.6, 149.8, 149.0, 148.8, 146.0 (6 x **C**-OCH$_3$), 128.7, 126.7, 125.1, 124.3, 121.8, 120.4 (**C6a, C9, C10a, C3, C1'', C3''**), 114.3 (**C**H-C3), 111.9 (**C6''**), 61.2, 60.6, 60.5, 60.1, 60.0, 56.0 (6 x O**C**H$_3$), 51.9 (**C11a**), 50.8 (**C6**), 21.8, 20.8 (**C11, C1'**), 11.2 (**C2'**), 9.7, 9.4 (2 x **C**H$_3$-CAr).

5.3.9.15. Synthesis of (*Z*)-7,8,10-trimethoxy-9-methyl-6-phenyl-3-(2,4,5-trimethoxy-3-methylbenzylidene)-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 21p.



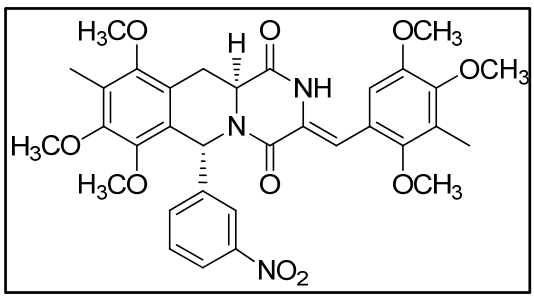
Obtained according to the general procedure **4.3.9** using compound **20c** (0.2 g, 0.39 mmol) and benzaldehyde (0.1 mL, 0.98 mmol) as starting materials, *p*-toluene sulfinic acid (0.079 g, 0.51 mmol), and toluene (2.0 mL) as solvent at 140 ºC. Purification by flash column chromatography on silica gel using 8:2 petroleum ether:diethyl ether as eluent afforded product **21p** (0.18 g, 0.32 mmol) as a yellow solid in 83% yield as a mixture of amide rotamers in $CDCl_3$, 25 ºC; **Mp** 109–111 ºC; **IR (NaCl) ν_{max}** 2938, 2360, 1694, 1624 cm^{-1}; **Analysis:** Calcd. for $C_{33}H_{36}N_2O_8$: C, 67.33; H, 6.16; N, 4.76. Found: C, 67.39; H, 6.11; N, 4.67; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.37 (s, 1H,C**H**Ar), 7.25 – 7.12 (m, 8H, **H2', H6', H6, CH**-C3, **NH**), 4.35 (dd, *J* = 12.6, 4.4 Hz, 1H, **H11a**), 3.80 – 3.77 (m, 6H, **OCH$_3$**), 3.73 (s, 3H, **OCH$_3$**), 3.68 (s, 3H, **OCH$_3$**), 3.52 – 3.46 (s, 3H, **OCH$_3$, H11a**), 3.39 (s, 3H, **OCH$_3$**), 2.80 (dd, *J* = 16.6, 12.6 Hz, 1H, **H11a**), 2.21 (s, 3H, **CH$_3$**), 2.20 (s, 3H, **CH$_3$**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.5 (**C1**), 157.5 (**C4**), 153.7, 153.5, 152.2, 151.9, 151.8, 150.7, 146.4, 146.0, 140.4 (**C**-OCH$_3$), 128.7, 128.6, 128.3, 128.0 (**CH**-C3, **C1'-C5'**), 125.9, 125.9, 125.6, 125.1, 125.0, 124.8, 121.8, 118.7, 118.7 (**C3**, **C6a**, **C9**, **C10a, C**-Ar, **C**-CH$_3$), 111.3, 111.2 (**CH**-Ar) 62.3, 60.3, 60.2, 60.2, 60.1, 60.0, 59.7 (O**C**H$_3$), 52.1, 52.1, 51.8 (**C6**), 29.8, 29.8 (**C11**), 9.5, 9.5 (**CH$_3$**).

5.3.9.16. Synthesis of (*Z*)-6-(4-bromophenyl)-7,8,10-trimethoxy-9-methyl-3-(2,4,5-trimethoxy-3-methylbenzylidene)-2,3,11,11a-tetrahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 21q.



Obtained according to the general procedure **4.3.9** using compound **20c** (0.1 g, 0.19 mmol) and 4-bromobenzaldehyde (0.07 g, 0.38 mmol) as starting materials, *p*-toluene sulfinic acid (0.050 g, 0.32 mmol), and toluene (1.0 mL) as solvent at 140 ºC for 24 h. Purification by flash column chromatography on silica gel using 8:2 petroleum ether:diethyl ether as eluent afforded product **21q** (0.11 g, 0.16 mmol) as a brown solid in 85% yield; **Mp** 115–117 ºC; **IR (NaCl) ν_{max}** 2935, 2360, 1693, 1626 cm^{-1}; **Analysis**: Calcd. for $C_{33}H_{35}N_2O_8$: C, 59.37; H, 5.28; N, 4.20 Found: C, 59.31; H, 5.11; N, 4.15; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 9.38 (s, 1H, N**H**), 7.44 (d, *J* = 8.4 Hz, 2H, **H3',H5'**), 7.19 (s, 1H, **H6**), 7.15 (d, *J* = 8.4 Hz, 2H, **H2', H6'**), 6.96 (s, 1H, **CH**-C3), 6.63 (s, 1H, **CH**-Ar), 4.29 (dd, *J* = 12.4, 4.5 Hz, 1H, **H11a**), 3.82 (s, 3H, OC**H$_3$**) 3.81 (s, 3H, OC**H$_3$**), 3.75 (s, 3H, OC**H$_3$**), 3.70 (s, 3H, OC**H$_3$**), 3.61 (s, 3H, OC**H$_3$**), 3.59 – 3.52 (m, 1H, **H11**), 3.48 (s, 3H, OC**H$_3$**), 2.86 (dd, *J* = 16.9, 12.5 Hz, 1H, **H11**), 2.22 (s, 6H, **CH$_3$**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.9 (**C1**), 157.2 (**C4**), 152.3, 150.7, 149.8, 149.0, 148.9 (**C**-OCH_3), 146.2 (**C7**), 140.0 (**C1'**), 131.8 (**C3', C5'**), 130.2 (**C2', C6'**), 126.7 (**C**-Me), 125.5* (**C3**), 125.1** (**C4'**), 124.9 (**C**-Me), 122.3* (**C1''**), 121.8**, 121.7** (**C6a, C10a**), 114.4 (**C**H-C3), 112.0 (**C**H-Ar), 61.3, 60.5, 60.2, 60.1, 59.8, 56.0 (6 x O**C**H_3), 51.9 (**C11a**), 51.6 (**C6**), 29.1 (**C11**), 9.7, 9.6 (**C**H_3).

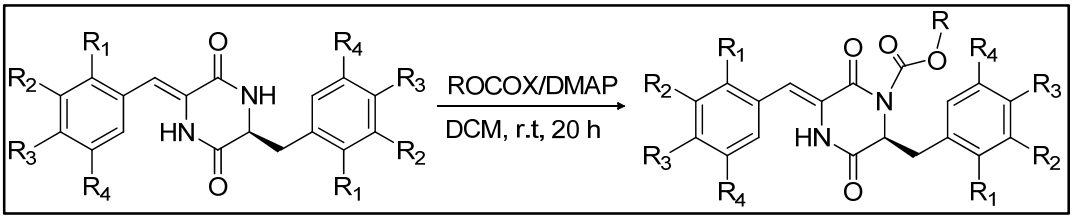
5.3.9.17. Synthesis of (*Z*)-7,8,10-trimethoxy-9-methyl-6-(3-nitrophenyl)-3-(2,4,5-trimethoxy-3-methylbenzylidene)-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 21r.



Obtained according to the general procedure **4.3.9** using compound **20c** (0.1 g, 0.19 mmol) and 3-nitrobenzaldehyde (0.057 g, 0.69 mmol) as starting materials, *p*-toluene sulfinic acid (0.050 g, 0.32 mmol), and toluene (1.0 mL) as solvent at 140 ºC for 24 h. Purification by flash column chromatography on silica gel using 8:2 petroleum ether:diethyl ether as eluent afforded product **21r** (0.088 g, 0.13 mmol) as a

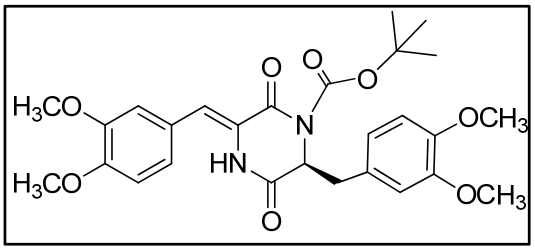
brown solid in 71% yield as a mixture 1:1 of rotamers in $CDCl_3$, 25 ºC; **Mp** 118–120ºC; **IR (NaCl)** ν_{max} 3200, 2936, 2360, 1689, 1627 cm^{-1}; **Analysis**: Calcd. for $C_{33}H_{35}N_3O_{10}$: C, 62.55; H, 5.57; N, 6.63. Found: C, 62.50; H, 5.51; N, 6.53; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 9.61 (s, 0.5H, N**H**), 9.45 (s, 0.5H, N**H**), 8.19-8.14 (m, 1H, **C6'**), 8.08 – 8.07 (m, 1H, **C2'**), 7.75-7.64 (m, 1H, **C4'**), 7.58 – 7.46 (m, 1H, **C5'**), 7.28 (s, 1H, **C6**), 6.99 (s, 0.5H, C**H**-C3), 6.89 (s, 0.5H, C**H**-C3), 6.68 (s, 0.5H, C**H**-Ar), 6.64 (s, 0.5H, C**H**-Ar), 4.23 (dd, *J* = 12.3, 4.5 Hz, 1H, **C11a**), 3.82 – 3.52 (m, 19H, OC**H$_3$**, **H11**), 2.88 (dd, *J* = 16.8, 12.5 Hz, 1H, **H11**), 2.26 – 2.22 (m, 6H, C**H$_3$**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.7 (**C1**), 157.5 (**C4**), 152.5, 150.8, 149.8, 149.3, 149.1, 149.0, 148.5, 146.2 (6 x **C**-OCH_3), 142.9 (**C7**), 134.5 (**C1'**), 129.7*, 126.8*, 126.1*, 125.5*, 124.6*, 124.0* (2 x **C**-Me**, C1', C3, C6a, C10a**), 123.3, 123.2 (**C2',C6'**), 121.7*, 121.7*, 121.6* (**C3'**), 115.0, 114.0 (**C**H-C3), 112.3*, 112.0* (**C**H-Ar), 61.4, 61.2, 60.5, 60.5, 60.3, 60.1, 59.9, 56.0 (O**C**H_3), 52.3 (**C11a**), 51.4 (**C6**), 29.0 (**C11**), 9.7, 9.6, 9.6 (2 x **C**H_3).

5.3.10. General procedure to obtain (±)-(*Z*)-6-dimethoxybenzyl-3-dimethoxybenzylidene-1-*tert*-butyloxicarbonyl-2,5-piperazinedione 21a–21d.



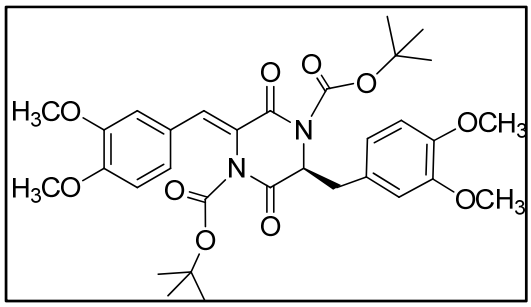
To compound **19** (1.0 eq) was added DMAP (0.5 eq), $(Boc)_2O$ or ethyl chloroformate (1.0 – 2.2 eq) and DCM at room temperature for 20 h. The reaction mixture was extracted with DCM (3 x 20 mL), the organic layer was dried over anhydrous Na_2SO_4 and was filtered. The solution was concentrated *in vacuo* and was purified by flash column chromatography using a mixture of petroleum ether: diethyl ether as eluent to obtain compounds **21a – 21d**.

5.3.10.1. Synthesis of (±)-(*Z*)-6-(3,4-dimethoxybenzyl)-3-(3,4-dimethoxybenzylidene)-1-*tert*-butyloxicarbonyl-2,5-piperazinedione 22a.



Obtained according to the general procedure **4.3.10** using compound **20a** (5.0 g, 0.012 mol), as starting material, DMAP (0.73 g, 5.9 mmol), $(Boc)_2O$ (2.59 g, 0.012 mol) and DCM (100 mL) as solvent. Purification by flash column chromatography on silica gel using 6:4 petroleum ether:diethyl ether as eluent afforded product **22a** (0.076 g, 0.135 mmol) as a yellow solid in 58% yield. **M.p**: 71-73 ºC. **IR (NaCl) ν_{max}**: 3290.1 (NH), 1772.0 (CO-N-CO-O), 1699.0 (N-CO), 1636.7 (N-CO), 1239.3 (C-O) cm^{-1}. **Analysis:** Calcd. for $C_{27}H_{32}N_2O_8$:C 63.27, H 6.29, N 5.47. Found: C 63.20, H 6.23, N 5.43. **^{1}H-RMN** (250 MHz, $CDCl_3$) δ: 7.69 (sa, 1H, N**H**), 6.55 (d, 1H, *J* = 8.4 Hz, C**H**$_{Ar}$, C**H**-C3), 6.47 (dd, 1H, *J* = 8.4 y 1.6 Hz, **H6'**), 6.40-6.36 (m, 3H, C**H**$_{Ar}$), 6.32-6.30 (m, 2H, C**H**$_{Ar}$), 4.73 (t, 1H *J* = 4.6 Hz, **H6**), 3.60 (s, 3H, OC**H**$_3$), 3.59 (s, 3H, OC**H**$_3$), 3.48 (s, 3H, OC**H**$_3$), 3.37 (s, 3H, OC**H**$_3$), 2.98 (dd, 1H, *J* = 14.0 y 4.9 Hz, C6-C**H**$_2$), 2.88 (dd, *J* = 14.0, 4.6 Hz, 1H, C6-C**H**$_2$), 1.27 (s, 9H, $CO_2C(CH_3)_3$).**^{13}C-RMN** (63 MHz, $CDCl_3$) δ: 166.3 (**C4**), 159.7 (**C1**), 151.4 (**C3'**), 149.9 (**C**OOC$(CH_3)_3$), 149.5, 149.2 y 149.0 (**C3''**, **C4''**, **C4'**), 126.7 (**C1'**), 125.6 (**C1''**), 124.6 (**C6**), 123.0 (**C6'**), 121.4 (**C6''**), 119.5 (**C**H-C3), 113.8 (**C2'**), 112.4, 111.9, 111.5 (**C2''**, **C5''**, **C5'**), 84.7 (COO**C**$(CH_3)_3$), 60.7 (**C6**), 56.2, 56.1 y 56.0 (4 x O**C**H_3), 39.3 (**C**H_2-C6), 28.3 (COOC(**C**$H_3)_3$).

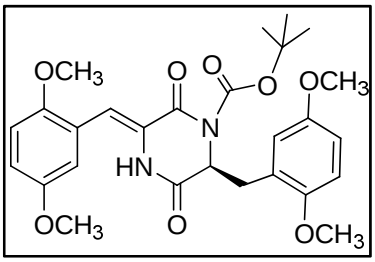
5.3.10.2. Synthesis of (±)-(*Z*)-6-(3,4-dimethoxybenzyl)-3-(3,4-dimethoxybenzylidene)-1-*tert*-butyloxicarbonyl-2,5-piperazinedione 22b.



Obtained according to the general procedure **4.3.10** using compound **20a** (5.0 g, 0.012 mol) as starting material, DMAP (1.46 g, 11.8 mmol), Et_3N (1.67 mL, 0.012 mol), $(Boc)_2O$ (7.77 g, 0.036 mol) and DCM (100 mL) as solvent. Purification by flash column chromatography on silica gel using petroleum ether as eluent afforded

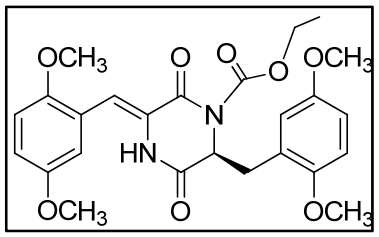
product **21a** (0.076 g, 0.135 mmol) as a yellow oil in 58 % yield. **IR (NaCl) ν_{max}:** 1777.6, 1693.0, 1263.0 y 1239.1 cm^{-1}. **Analysis:** Calcd. for $C_{32}H_{40}N_2O_{10}$: C 62.73, H 6.58, N 4.57. Found: C 62.82, H 6.61, N 4.50**.** **^{1}H-RMN** (250 MHz, $CDCl_3$) δ: 7.01 (s, 1H, C**H**-C6), 6.94 (dd, 1H, *J* = 8.4 y 1.9 Hz, **H6'**), 6,88-6.76 (m, 2H, **H2'**, **H5'**), 6.59 (dd, 1H, *J* = 8.1 y 1.9 Hz, **H6''**), 6.53 (d, 1H, *J* = 1.9 Hz, **H2''**), 6.47 (d, 1H, *J* = 8.1 Hz, **H5''**), 5.10 (t, 1H, *J* = 6.4 Hz, **H3**), 3.84 (s, 6H, 2 x O**C**H_3), 3.76 (s, 3H, O**C**H_3), 3.51 (s, 3H, O**C**H_3), 2.12 (d, 2H, *J* = 6.4 Hz, C3-CH_2), 1.38 (s, 9H, $CO_2C(CH_3)_3$), 1.01 (s, 9H, $CO_2C(CH_3)_3$).**^{13}C-RMN** (63 MHz, $CDCl_3$) δ: 165.8 (**C4**), 161.5 (**C1**), 149.6 (**C**OOC$(CH_3)_3$), 149.0, 147.9, 147.8, 147.3 (**C3'**, **C3''**, **C4'**, **C4''**), 146.1 (**C**OOC$(CH_3)_3$), 130.7 (**C**H–C3), 125.9 (**C1'**), 124.7, 122.8 (**C1'', C6**), 122.7 (**C6''**), 120.3 (**C6'**), 111.6 (**C2''**), 110.7 (**C5''**), 110.6, 110.4 (**C2'**, **C5'**), 83.9, 83.4 (2 x COO**C**$(CH_3)_3$), 61.1 (**C3**), 55.0, 54.9, 54.8, 54.6 (4 x O**C**H_3), 37.0 (**C**H_2–C6), 26.8, 26.2 (2 x $CO_2C(CH_3)_3$).

5.3.10.3. Synthesis of (±)-(*Z*)-6-(2,5-dimethoxybenzyl)-3-(2,5-dimethoxybenzylidene)-1-*tert*-butyloxicarbonyl-2,5-piperazinedione 22c.



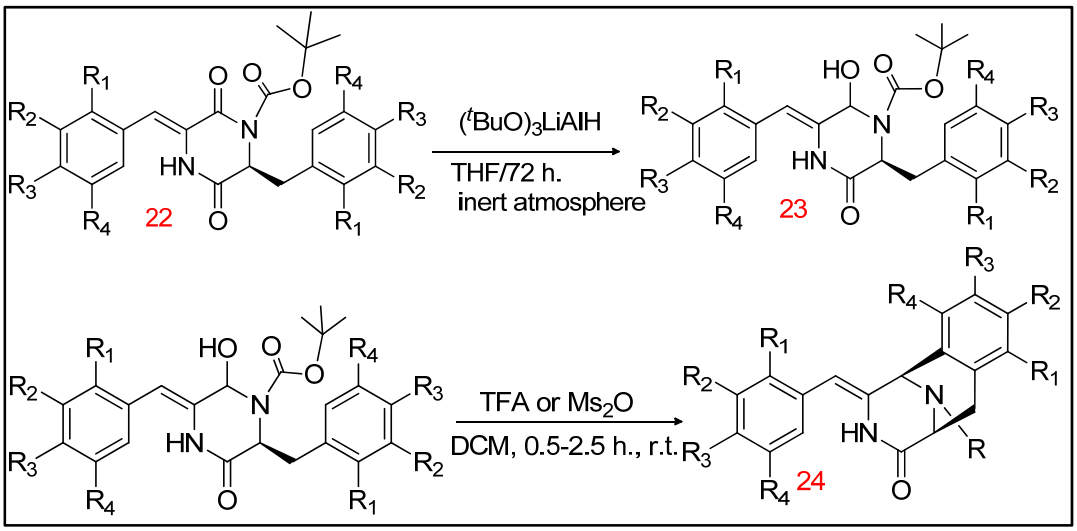
Obtained according to the general procedure **4.3.10** using compound **20b** (5.0 g, 0.012 mol) as starting material, DMAP (0.73 g, 5.9 mmol), $(Boc)_2O$ (2.59 g, 0.012 mol) and DCM (100 mL) as solvent. Purification by flash column chromatography on silica gel using 1:9 petroleum ether:diethyl ether as eluent afforded product **22c** (0.076 g, 0.135 mmol) as a yellow solid in 58% yield; **Mp** 132 – 133ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis:** Calcd. for $C_{27}H_{32}N_2O_8$: C, 63.27; H, 6.29; N, 5.47. Found: C, 63.26; H, 6.17 ; N, 5.52; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.39 (s, 1H, N**H**), 6.80 (s, 2H, **H3', H4'**), 6.65 (dd, *J* = 9.0, 2.7 Hz, 1H, **H4''**), 6.59 (d, *J* = 8.9 Hz, 1H, **H3''**), 6.55 (s, 1H, H6'), 6.51 (s, 1H, C**H**-C3), 6.49 (d, *J* = 2.6 Hz, 1H, **H6''**), 5.00 (t, *J* = 4.6 Hz, 1H, **H6**), 3.74 (s, 6H, 2 x O**C**H_3), 3.62 (s, 3H, O**C**H_3), 3.55 (dd, *J* = 13.6, 5.6 Hz, 1H, CH_2-C6), 3.37 (s, 3H, OCH_3), 2.92 (dd, *J* = 13.5, 4.0 Hz, 1H, CH_2-C6), 1.50 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 165.7 (**C4**), 158.8 (**C1**), 153.8, 153.2, 152.4, 150.6, 150.1 (4x **C**-OCH_3, **C**OC(CH_3)$_3$), 126.0* (**C1'**), 123.4 (**C1''**), 122.9* (**C3**), 117.1 (**C6''**), 116.4 (**C6'**), 115.5, 115.3 (***C4', *C**H**-C6), 114.1 (**C3''**), 113.7 (**C3'**), 111.0 (**C4''**), 83.5 (C(CH_3)$_3$), 59.8 (**C6**), 56.9, 55.6, 55.5, 55.0 (4xO**C**H_3), 33.1 (**C**H_2-C3), 27.9 (C(**C**H_3)$_3$).

5.3.10.4. Synthesis of (±)-(Z)-6-(2,5-dimethoxybenzyl)-3-(2,5-dimethoxybenzylidene)-1-ethoxicarbonyl-2,5-piperazinedione 22d.



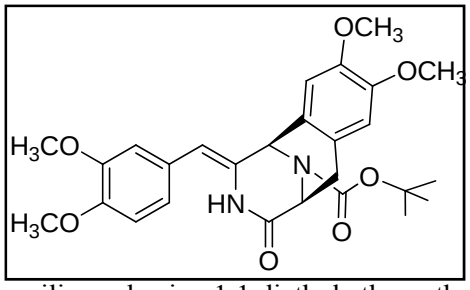
Obtained according to the general procedure **5.3.10** using compound **20b** (2.0 g, 0.0047 mol) as starting material, DMAP (0.57 g, 0.0047 mol), Et_3N (0.65 mL, 0.0047 mol), ethyl chloroformate (1.0 mL, 0.010 mol) and DCM (10 mL) as solvent at 50 ºC for 12 h., then 70 ºC for 2 h. Purification by flash column chromatography on silica gel using 1:1 diethyl ether: ethyl acetate as eluent afforded product **22d** (0.369 g, 0.76 mmol) as a yellow solid in 16% yield.; **Mp** 143–144 ºC; **IR(NaCl) ν_{max}** 3180, 2910, 1689, 1627 cm^{-1}; **Analysis: Calcd.** for $C_{25}H_{28}N_2O_8$: C, 61.97; H, 5.83; N, 5.78 Found: C, 61.77; H, 5.80; N, 5.62.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.42 (s, 1H, N**H**), 6.90* (s, 1H, **H4'**), 6.89* (s, 1H, **H3'**), 6.74* (dd, *J* = 8.9, 2.9 Hz, 1H, **H4''**), 6.67 (d, *J* = 8.9 Hz, 1H, **H3''**), 6.62* (td, *J* = 1.8, 0.7 Hz, 1H, C**H-C6**), 6.58* (t, *J* = 0.6 Hz, 1H, **H6'**), 6.56* (d, *J* = 2.9 Hz, 1H, **H6''**), 5.17 (ddd, *J* = 5.7, 3.7, 1.2 Hz, 1H, **H3**), 4.39 (q, *J* = 7.0 Hz, 2H, OC**H$_2$**), 3.84 (s, 3H, OC**H$_3$**), 3.83 (s, 3H, OC**H$_3$**), 3.70 (s, 3H, OC**H$_3$**) 3.65 (dd, *J* = 13.7, 5.7 Hz, 1H, C**H$_2$**-C3), 3.44 (s, 3H, OC**H$_3$**), 3.02 (dd, *J* = 13.6, 3.7 Hz, 1H, C**H$_2$**-C3), 1.41 (t, *J* = 7.1 Hz, 3H, C**H$_3$**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 165.6 (**C4**), 158.7 (**C2**), 154.0, 153.4 (2x**C**-OCH_3), 152.9 (N-**C**O), 152.5, 150.3 (2x**C**-OCH_3), 126.0** (**C3**), 123.4 (**C1''**), 123.0** (**C1'**), 117.2 (**C6''**) , 116.6*, 115.8*, 115.8* (**C3', C4', C6'**), 114.4 (**C4''**), 114.0* (**C**H-**C6**), 111.2 (**C3''**), 63.6 (O-C**H$_2$**), 60.0 (**C6**), 57.2, 55.9, 55.6, 55.3 (4xO**C**H_3), 33.2 (**C**H_2-C6), 14.4 (C**H$_3$**).

5.3.11. General procedure to obtain 2-benzylidene-1,5-epiminobenzo[*d*]azocines 24a – 24e.



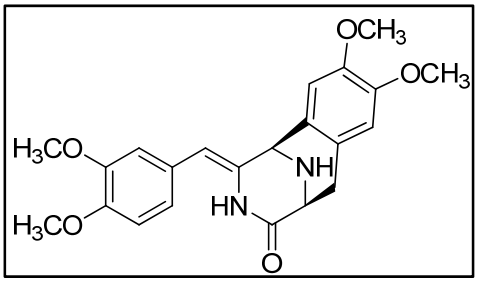
(^{t}BuO)LiAlH (5.0 eq) was added under an Ar atmosphere to a solution of compound **22** (1.00 eq) in THF (53 eq) at room temperature and stirred for 12-72 h. The reaction was poured into a saturated solution of $NaHCO_3$ and was filtered through celite. The celite pad was washed with DCM (3 x 20 mL) and the mixture was extracted with DCM (2 x 10 mL). The organic layer was dried over anhydride Na_2SO_4 and was filtered. The solution was evaporated *in vacuo* to obtain a pale yellow solid which was used immediately in the next reaction due to its unstability. To the solid was added TFA (46 eq) or Ms_2O (2.6 eq) and DCM (34.0-48.0 eq) under an Ar atmosphere to 25 – 40 ºC and stirred for 0.5 – 2.5 h. The crude was quenched with a saturate solution of $NaHCO_3$ and extracted with DCM (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo* to obtain compounds **24a-24e**.

5.3.11.1. Synthesis of (±)-(1*R**, 5*S**, *Z*) *tert*-butyl 8,9-dimethoxy-2-(3,4-dimethoxybenzylidene)-4-oxo-2,3,5,6-tetrahydro-1,5-imino-1*H*-[3]benzazocin-11-carboxylate 24a.



Obtained according to the general procedure **5.3.11** using compound **22a** (3.4 g, 6.6 mmol) as starting material (^{t}BuO)LiAlH (8.51 g, 0.034 mol), and THF (60.0 mL) as solvent for 72 h. Then, Ms_2O (2.89 g, 0.017 mol) and DCM (2.0 ml) as solvent was added and stirred for 0.5 h. Purification by flash column chromatography on silica gel using 1:1 diethyl ether: ethyl acetate as eluent afforded product **24a** (1.0 g, 2.1 mmol) as a white solid in 32% yield. as a 4:1 mixture of amide rotamers in $CDCl_3$, 25 ºC; **Mp** 197–198 ºC; **IR(NaCl) ν_{max}** 3050, 2930, 2359, 1693 cm^{-1}; **Analysis: Calcd.** for $C_{27}H_{32}N_2O_8$: C, 65.31; H, 6.50; N, 5.64 Found: C, 65.20; H, 6.63; N, 5.58.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.66 (bs, 0.8H, N**H**), 7.60 (bs, 0.2H, N**H**), 6.82 – 6.72 (m, 3H, **H10, H5', H6'**), 6.66 (d, *J* = 1.3 Hz, 1H, **H2'**), 6.57 (bs, 1H, **H7**), 5.87 (s, 0.8H, C**H**-C2), 5.84 (s, 0.2H, C**H**-C2), 5.63 (s, 0.7H, **H1**), 5.42 (s, 0.3H, **H1**), 5.12 (s, 1H, **H5**), 4.99 (s, 1H, **H5**), 3.85 (s, 3H, OC**H$_3$**), 3.83 (s, 6H, OC**H$_3$**), 3.81 (s, 3H, OC**H$_3$**), 3.25 (dd, *J* = 16.7, 6.5 Hz, 1H, **H6**), 3.00 (d, *J* = 17.0 Hz, 1H, **H6**), 1.46 (s, 9H, OC(C**H$_3$**)$_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 169.2 (**C4**), 152.6 (O**C**OC(CH$_3$)$_3$), 149.4, 149.1, 148.3, 147.9 (4x**C**-OCH$_3$), 134.5, 126.4, 125.9, 123.8 (**C10a, C6a, C1', C2**), 120.5 (**C6'**), 111.5, 111.4 (**C2', C7, C10**), 109.9 (**C5'**), 105.2 (**C**H-C2), 81.4 (**C**(CH$_3$)$_3$), 56.2, 55.9 (4xO**C**H$_3$), 53.7 (**C5**), 52.9 (**C1**), 31.4 (**C6**), 28.3 (OC(**C**H$_3$)$_3$).

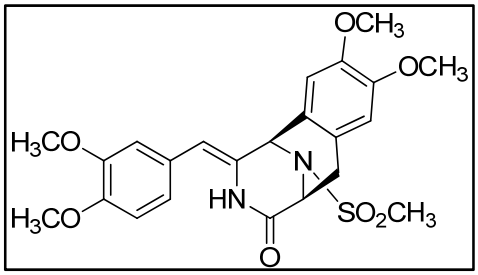
5.3.11.2. Synthesis of (±)-(1*R**, 5*S**, *Z*)-8,9-dimethoxy-2-(3,4-dimethoxybenzylidene)-2,3,5,6-tetrahydro-1,5-imino-[3]benzazocin-4(1*H*)-one 24b.



Obtained according to the general procedure **5.3.11** using compound **22a** (3.4 g, 6.6 mmol) as starting material, (^{t}BuO)LiAlH (8.51 g, 0.034 mol), and THF (60 mL) as solvent for 72 h. Then, TFA (23.3 mL, 0.304 mol) and DCM (15 mL) as solvent was added and stirred for 2 h at room temperature and then 0.5 h at 40 ºC. Purification by flash column chromatography

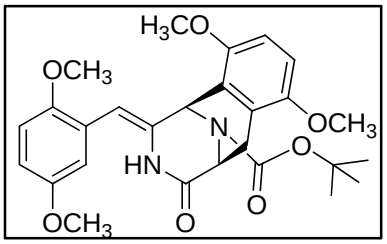
on silica gel using 95:5 ethyl acetate:methanol as eluent afforded product **24b** (2.6 g, 6.5 mmol) as a white solid in 99% yield; **Mp** 124–125 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693 cm^{-1}; **Analysis:** Calcd. for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.55; H, 6.22; N, 7.09; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.77 (s, 1H, **H3**), 6.71* (s, 1H, **H6'**), 6.70* (s, 1H, **H2'**), 6.66 (s, 1H, **H10**), 6.61* (d, *J* = 2.2 Hz, 1H, **H5'**), 6.50 (s, 1H, **H7**), 5.66 (s, 1H, C**H**-C2), 4.42 (s, 1H, **H1**), 3.93 (d, *J* = 5.9 Hz, 1H, **H5**), 3.79 – 3.73 (m, 12H, 4xOC**H$_3$**), 3.14 (dd, *J* = 16.6, 6.5 Hz, 1H, **H6**), 2.86 (d, *J* = 16.6 Hz, 1H, **H6**), 2.83 (bs, 1H, N**H**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 171.3 (**C4**), 149.1, 148.7, 147.9, 147.4 (4x**C**-OCH_3), 137.2, 126.5 (**C10a, C1', C2**), 124.2 (**C6a**), 120.4 (**C6'**), 112.0 (**C2'**), 111.3 (**C5'**), 111.2 (**C7**), 109.9 (**C10**), 103.2 (**C**H-C2), 56.0, 55.7 (4xO**C**H_3), 54.5 (**C1**), 53.3 (**C5**), 32.0 (**C6**).

5.3.11.3. Synthesis of (±)-(1*R**, 5*S**, *Z*)-8,9-dimethoxy-2-(3,4-dimethoxybenzylidene)-11-(methylsulfonyl)-2,3,5,6-tetrahydro-1,5-imino-[3]benzazocin-4(1*H*)-one 24c.



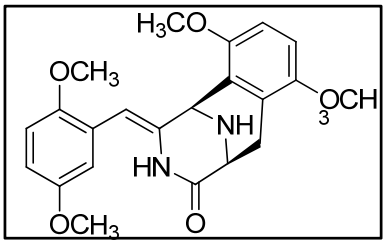
Obtained according to the general procedure **5.3.11** using compound **22a** (3.4 g, 6.6 mmol) as starting material (^{t}BuO)LiAlH (8.51 g, 0.034 mol), and THF (60 mL) as solvent for 72 h. Then, Ms_2O (2.89 g, 0.017 mol) and DCM (2.0 mL) as a solvent was added and stirred for 2.5 h. Purification by flash column chromatography on silica gel using 1:1 diethyl ether:ethyl acetate as eluent afforded product **24c** (0.76 g, 1.6 mmol) as a pale brown solid in 24% yield as a mixture of amide rotamers in $CDCl_3$, 25 ºC. **Mp** 200–201 ºC; **IR (NaCl) ν_{max}** 3000, 2900, 1603, 1550 cm^{-1}; **Analysis:** Calcd. for $C_{23}H_{26}N_2O_7$: C, 58.22; H, 5.52; N, 5.90; S, 6.76. Found: C, 58.09; H, 5.40; N, 5.79; S, 6.70; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.79 (s, 1H, N**H**), 7.06 – 6.51 (m, 5H, C**H$_{Ar}$**), 5.95 (s, 1H, C**H**-C2), 4.74 (dd, *J* = 16.8, 6.4 Hz, 1H, **H5**), 3.94 – 3.80 (m, 12H, 4xOC**H$_3$**), 3.48 (s, 1H, **H1**), 3.40 (dd, *J* = 16.4, 6.3 Hz, 1H, **H6**), 3.10 (d, *J* = 17.0 Hz, 1H, **H6**), 3.00 – 2.99 (s, 0.3H, SO_2C**H$_3$**), 2.96 (s, 0.7H, SO_2C**H$_3$**), 2.94 (s, 1.8H, SO_2C**H$_3$**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 168.5, 167.8 (**C**O), 149.6, 149.5, 149.4, 149.1, 148.8, 148.4, 148.2, 148.0 (4x**C**-OCH_3), 135.5*, 133.4* (**C2**), 127.2*, 125.7* (**C10a**), 125.2*, 124.6* (**C1'**), 123.3*, 122.4* (**C6a**), 121.2, 120.4 (**C**H_{Ar}), 111.8, 111.6 (**C**H_{Ar}), 111.5, 111.3 (**C**H_{Ar}), 111.0, 109.6 (**C**H_{Ar}), 108.8 (**C**H_{Ar}), 108.7, 106.3 (**C**H-C2), 56.3, 56.0, 56.0, 55.9, 55.6, 55.4 (4xO**C**H_3), 54.2, 53.8 (**C5**), 39.1, 38.9 (SO_2**C**H_3), 32.4, 31.6 (**C6**).

5.3.11.4. Synthesis of (±)-(1*R**, 5*S**, *Z*) *tert*-butyl 7,10-dimethoxy-2-(2,5-dimethoxybenzylidene)-4-oxo-2,3,5,6-tetrahydro-1,5-imino-1*H*-[3]benzazocin-11-carboxylate 24d.



Obtained according to the general procedure **5.3.11** using compound **22c** (3.4 g, 6.6 mmol), as starting material (^{t}BuO)LiAlH (8.51 g, 0.034 mol), and THF (60 mL) as solvent for 72 h. Then, Ms_2O (2.89 g, 0.017 mol) and DCM (2.0 mL) as a solvent was added and stirred for 0.5 h. Purification by flash column chromatography on silica gel using 1:1 diethyl ether: ethyl acetate as eluent afforded product **24d** (0.99 g, 2.0 mmol) as a white solid in 30% yield.; **Mp** 192–193 ºC; **IR (NaCl) ν_{max}** 3180, 2910, 1689, 1627 cm^{-1}; **Analysis:** Calcd**.** for $C_{27}H_{32}N_2O_7$: C, 65.31; H, 6.50; N, 5.64. Found: C, 65.40; H, 6.50; N, 5.62.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.29, 8.09 (s, 1H, N**H**), 6.76-6.61 (m, 5H, C$\mathbf{H}_{Ar}$), 6.12-5.90 (m, 2H, C**H**-C2, **H1**), 5.44-5.13 (m, 1H, **H5**), 3.726-3.66 (m, 12H, 4xOC$\mathbf{H}_3$), 3.19-2.92 (m, 2H, **H6**), 1.43 (s, 9H, C-(C$\mathbf{H}_3$)$_3$).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 168.9 (**C4**), 153.6 (N**C**O), 153.2, 152.3 (**C**-OCH_3), 151.0 (**C7**), 149.9 (**C**-OCH_3), 132.7 (**C2**), 124.2 (**C1'**), 123.4, 123.1 (**C6a**), 122.3, 121.8 (**C10a**), 115.8 (**C6'**), 112.9, 108.6, 108.2, 103.6, 102.9 (6x**C**H_{Ar}), 80.8 (O**C**-$(CH_3)_3$), 56.0, 55.3, 55.2 (4xO**C**H_3), 52.4, 51.0 (**C5**), 50.0, 47.9 (**C1**), 28.1 (C-(**C**H_3)$_3$), 26.6 (**C6**).

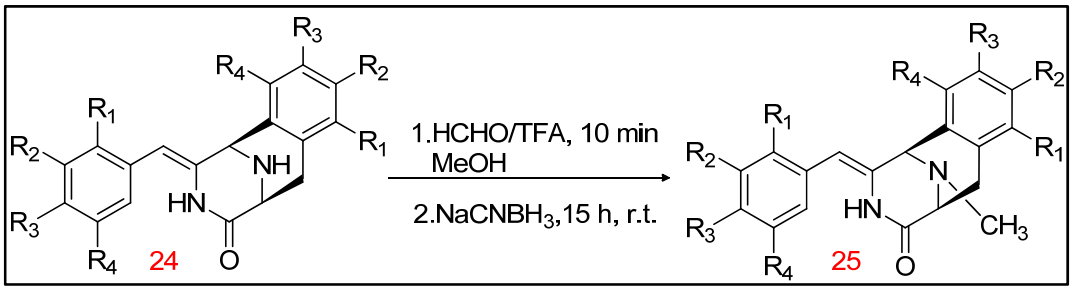
5.3.11.5. Synthesis of (±)-(1*R**, 5*S**, *Z*)-7,10-dimethoxy-2-(2,5-dimethoxybenzylidene)-2,3,5,6-tetrahydro-1,5-imino-[3]benzazocin 4(1*H*)-one 24e.



Obtained according to the general procedure **5.3.11** using compound **22c** (6.0 g, 0.012 mol) as starting material (^{t}BuO)LiAlH (14.9 g, 0.059 mol), and THF (50 mL) as solvent for 12 h. Then, TFA (50.0 mL, 0.65 mol) and DCM (30 mL) as a solvent was added and stirred for 2 h.at room temperature and then 0.5 h. at 40 ºC. Purification by flash column chromatography on silica gel using 95:5 ethyl acetate: methanol as eluent afforded product **24e** (4.6 g, 0.012 mol) as a white solid in 99% yield.; **Mp** 90–91 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}**; Analysis: Calcd.** for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.46; H, 5.96 ; N, 7.00.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.00 (s, 1H, **H3**), 6.86 – 6.65 (m, 5H, C$\mathbf{H}_{Ar}$), 5.94 (s, 1H, C**H**-C2), 5.04 (s, 1H, **H1**), 4.04 (d, *J* = 5.3 Hz, 1H, **H5**), 3.82 (s, 3H, OC$\mathbf{H}_3$), 3.75 (s, 3H, OC$\mathbf{H}_3$), 3.73 (s, 3H, OC$\mathbf{H}_3$), 3.72, 3.13 – 2.94 (m, 2H, **H6**), 2.58 (bs, 1H, **H11**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 171.3 (N**C**O), 153.8 (**C**-OCH_3), 151.4 (**C2'**), 150.5, 150.4 (2x**C**-

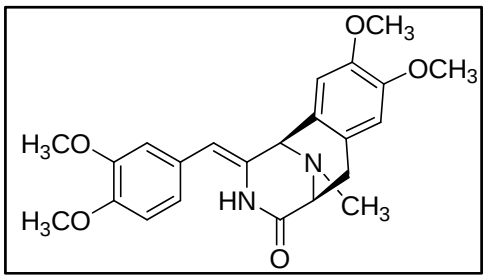
OCH_3), 136.4 (**C2**), 124.8, 124.7 (**C6a, C10a**), 122.7 (**C1'**), 115.9 (**C6'**), 113.0, 112.8 (**C3', C4'**), 108.5, 108.2 (**C8, C9**), 101.6 (**C**H-C2), 56.4, 55.8, 55.7, 55.6 (4x**O**CH_3), 52.4 (**C5**), 49.1 (**C1**), 27.6 (**C6**).

5.3.12. General procedure to obtain 2-benzylidene-11-methyl-2,3,5,6-tetrahydro-1,5-epiminobenzo[*d*]azocin 25a–25c.



To a solution of **24** (1.0 eq) in methanol (150 eq), formaldehyde 37% (3.2 eq) and TFA (1.6 eq) was added and the reaction was stirred for 10 min. Then, sodium cianoborohidride (2.0 eq) was added at room temperature and stirred for 15 – 48 h. The mixture was quenched with a saturated solution of $NaHCO_3$,extracted with DCM (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography using ethyl acetate as eluent to obtain **25a–25c.**

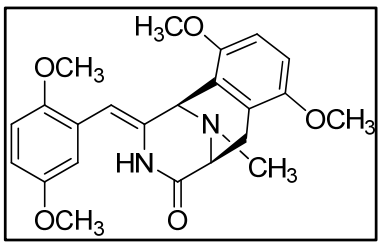
5.3.12.1. Synthesis of (±)-(1*R**, 5*S**, *Z*)-8,9-dimethoxy-2-(3,4-dimethoxybenzylidene)-11-methyl-2,3,5,6-tetrahydro-1,5-imino-[3]benzazocin-4(1*H*)-one 25a.



Obtained according to the general procedure **5.3.12** using compound **24b** (1.69 g, 4.30 mmol) as starting material, HCHO (1.02 mL, 13.2 mmol), $NaCNBH_3$ (0.53 g, 8.4 mmol), TFA (0.51 mL, 6.88 mmol) and MeOH (25 mL) as solvent for 15 h. Purification by flash column chromatography on silica gel using 95:5 ethyl acetate:methanol as eluent afforded product **25a** (1.06 g, 2.58 mmol) as a pale yellow solid in 60% yield as a 4:1 mixture of amide rotamers in $CDCl_3$, 25 ºC. **Mp** 89–90 ºC; **IR(NaCl)** ν_{max} 3200, 2930, 1693, 1625 cm^{-1}; **Analysis: Calcd.** for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82 Found: C, 67.22; H, 6.30; N, 6.79.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.74 (s, 1H, N**H**),

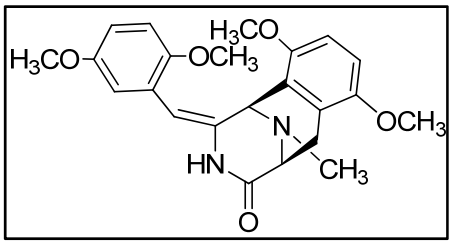
6.87 (s, 0.5H, C**H**$_{Ar}$), 6.76 (s, 1.5H, C**H**$_{Ar}$), 6.69 (s, 1H, C**H**$_{Ar}$), 6.64 (s, 1H, C**H**$_{Ar}$), 6.55 (s, 1H, C**H**$_{Ar}$), 6.49 (s, 0.8H, C**H**$_{Ar}$), 6.47 (s, 0.2H, C**H**$_{Ar}$), 5.85 (s, 0.1H, C**H**-C2), 5.77 (s, 0.9H, C**H**-C2), 4.13 (s, 1H, **H1**), 3.86 – 3.74 (m, 12H, 4xOC**H**$_3$), 3.61 (d, *J* = 6.8 Hz, 1H, **H5**), 3.27 (dd, *J* = 16.7, 6.6 Hz, 1H, **H6**), 2.90 (d, *J* = 16.6 Hz, 1H, **H6**), 2.59 (s, 0.75H, NC**H**$_3$), 2.57 (s, 0.35H, NC**H**$_3$), 2.54 (s, 1.90H, NC**H**$_3$); ^{13}**C NMR** (63 MHz, $CDCl_3$) δ 172.7, 170.6, 170.1 (**C4**), 149.3, 149.0, 148.7, 148.4, 148.3, 148.1, 148.0, 147.8, 147.6, 147.4 (4x**C**-OCH$_3$), 137.1, 134.8, 130.5 (**C1'**), 128.4*, 127.0*, 126.7* (**C10a**), 126.6*, 126.1*, 125.7* (**C6a**), 124.4*, 123.9*, 123.3* (**C2**), 121.3, 120.5 (**C**H$_{Ar}$), 112.3, 111.6, 111.5, 111.4 (**C**H$_{Ar}$), 111.2, 111.1, 110.8 (**C**H$_{Ar}$), 110.1, 109.2, 108.9 (**C**H$_{Ar}$), 106.0 (**C**H-C2), 63.6, 61.5 (**C1**), 60.0, 59.7 (**C5**), 56.1, 55.9, 55.8, 55.7, 55.4 (4xO**C**H$_3$), 41.4, 41.3 (N**C**H$_3$), 31.7, 31.6 (**C6**).

5.3.12.2. Synthesis of (±)-(1*R**, 5*S**, *E*)-7,10-dimethoxy-2-(2,5-dimethoxybenzylidene)-11-methyl-2,3,5,6-tetrahydro-1,5-imino-[3]benzazocin-4(1*H*)-one 25b.



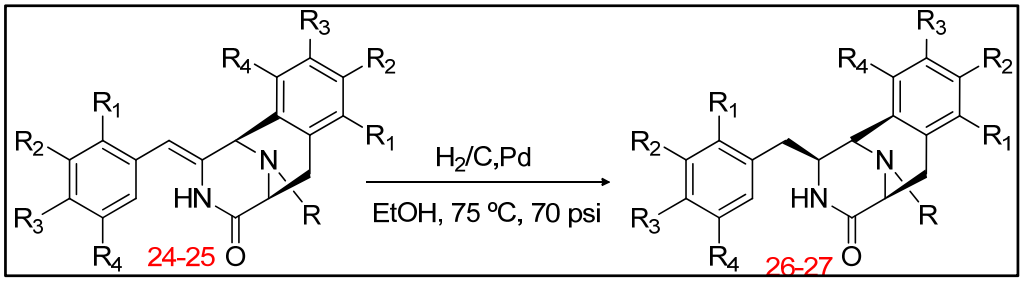
Obtained according to the general procedure **5.3.12** using compound **24e** (0.17 g, 0.44 mmol) as starting material, HCHO (0.12 mL, 1.41 mmol), $NaCNBH_3$ (0.055 g, 0.88 mmol), TFA (0.077g, 2.26 mmol) and MeOH (3.0 mL) as solvent for 48 h. Purification by flash column chromatography on silica gel using 95:5 ethyl acetate:methanol as eluent afforded product **25b** (0.10 g, 0.25 mmol) as a pale yellow solid in 57% yield. **Mp** 80–81ºC; **IR (NaCl)** ν_{max} 3200, 2930, 1693, 1625 cm^{-1}; **Analysis: Calcd.** for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82 Found: C, 67.46; H, 6.45; N, 7.01.; ^{1}**H NMR** (250 MHz, $CDCl_3$) δ 8.04 (s, 1H, N**H**), 6.82 – 6.67 (m, 6H, **H3', H4', H6', H8, H9**), 5.96 (s, 1H, C**H**-C2), 4.70 (s, 1H, **H1**), 3.82 (s, 3H, C2', -OC**H**$_3$, C10-OC**H**$_3$), 3.74 (s, 3H, C5'-OC**H**$_3$, C7-OC**H**$_3$), 3.73 (s, 3H, C5'-OC**H**$_3$, C7-OC**H**$_3$), 3.72 (s, 3H, C2'-OC**H**$_3$, C10-OC**H**$_3$), 3.67 – 3.63 (m, 1H, **H5**), 3.08 – 3.00 (m, 2H, **H6**), 2.58 (s, 3H, C**H**$_3$).; ^{13}**C NMR** (63 MHz, $CDCl_3$) δ 170.0 (N**C**O), 153.8 (**C5'**), 151.3 (**C7**), 150.4, 150.3 (**C2', C10**), 133.4 (**C2**), 124.7, 124.6, 122.2 (**C1', C6a, C10a**), 116.1 (**C6'**), 113.1, 112.7, 108.5, 108.2 (**C3', C4', C8, C9**), 104.1 (**C**H-C2), 59.0 (**C5**), 56.4 (**C1**), 55.7, 55.7, 55.6, 55.5 (4xO**C**H$_3$), 41.3 (**C**H$_3$), 27.2 (**C6**).

5.3.12.3. Synthesis of (E)-2-(2,5-dimethoxybenzylidene)-7,10-dimethoxy-11-methyl-2,3,5,6-tetrahydro-1,5-epiminobenzo[d]azocin-4(1H)-one 25c.



Obtained according to the general procedure **5.3.12** using compound **24e** (0.17 g, 0.44 mmol), HCHO (0.12 mL, 1.41 mmol), $NaCNBH_3$ (0.055 g, 0.88 mmol), TFA (0.077g, 2.26mmol) as starting material and MeOH (3.0 mL) as solvent for 48 h and then the crude was heated to 80 ºC for 3 h. Purification by flash column chromatography on silica gel using 95:5 ethyl acetate: methanol as eluent afforded product **25c** (0.075 g, 0.18 mmol) as a pale yellow solid in 44% yield. **Mp** 101–102 ºC; **IR(NaCl)** ν_{max} 3200, 2930, 1693, 1625 cm^{-1}; **Analysis:** Calcd. for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82 Found: C, 67.48; H, 6.40; N, 6.88.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.13 (s, 1H, N**H**), 6.79 – 6.70 (m, 6H, **H3', H4', H6', H8, H9**), 6.00 (s, 1H, C**H**-C2), 4.85 (s, 1H, **H1**), 3.83 – 3.74 (m, 13H, 4xOC**H$_3$**, **H5**), 3.13 (s, 2H, **H6**), 2.67 (s, 2H, C**H$_3$**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 168.8 (N**C**O), 153.9 (**C5'**), 151.2 (**C7**), 150.4 (**C2', C10**), 132.1 (**C2**), 124.4, 123.4, 121.6 (**C1', C6a, C10a**), 116.2 (**C6'**), 113.2, 113.1, 108.9, 108.6 (**C3', C4', C8, C9**), 105.4 (**C**H-C2), 58.9 (**C5**), 56.5 (**C1**), 55.8, 55.8, 55.7, 55.6 (4xO**C**H$_3$), 41.0 (**C**H$_3$), 27.0 (**C6**).

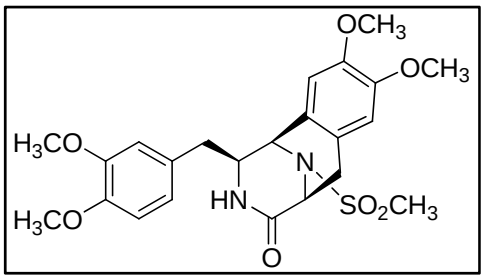
5.3.13. General procedure to obtain 2-benzyl-1,5-epiminobenzo[*d*]azocin 26-27.



To a solution of **24-25** (1.0 eq) in ethanol (100 mL) under an Ar atmosphere 10% Pd/C (50 % w/w) was added. The reaction was carried out under hydrogen (70 psi) and stirred for 3 h – 64 h. The crude was filtered through celite to remove the Pd/C, which was washed with

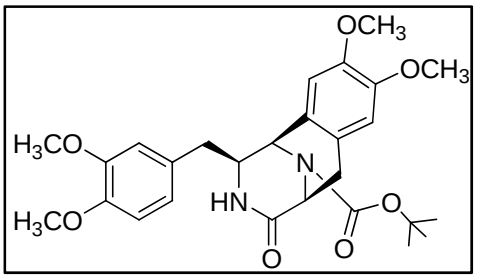
DCM (3 x 30 mL) to recover completely the reduced compounds. The organic layer was washed with saturated aqueous solution of $NaHSO_3$ (25 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to obtain **26-27.**

5.3.13.1. Synthesis of (±)-(1*R**, 2S*, 5*S**)-8,9-dimethoxy-2-(3,4-dimethoxybenzyl)-11-(methylsulfonyl)-2,3,5,6-tetrahydro-1,5-imino-[3]benzazocin-4(1*H*)-one 26a.



According to the general procedure **5.3.13** using compound **24c** (1.00 g, 2.1 mmol) as starting material, Pd/C (0.58 g), and EtOH (100 mL) as solvent for 3 h. Compound **26a** (0.95 g, 2.0 mmol) was obtained as a white solid in 95% yield as a mixture of rotamers in $CDCl_3$, 25 ºC. **Mp** 167 – 168 ºC; **IR(NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{23}H_{28}N_2O_7S$: C, 57.97; H, 5.92; N, 5.88; S, 6.73 Found: C, 65.00; H, 5.85; N, 5.59, S:6.80; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.82 (m, 2H, ***H2', *H5', *H6'**), 6.68 – 6.60 (m, 3H, ***H7, *H2', *H5', *H6'**), 6.55 (s, 1H, **H10**), 5.69 (d, *J* = 5.4 Hz, 1H, N**H**), 4.97 (d, *J* = 3.8 Hz, 1H, **H1**), 4.64 (d, *J* = 6.7 Hz, 1H, **H5**), 4.36 – 4.20 (m, 1H, **H2**), 3.86 (s, 3H, OC**H$_3$**),3.85 (s, 6H, OC**H$_3$**), 3.83 (s, 3H, OC**H$_3$**), 3.26 (dd, *J* = 17.4, 6.7 Hz, 1H, **H6**), 3.07 (d, *J* = 17.7 Hz, 1H, **H6**), 3.02 – 2.95 (m, 1H, C**H$_2$**-C2), 2.77 (s, 2.6H, SO_2C**H$_3$**), 2.71 (s, 0.4H, SO_2C**H$_3$**), 2.18 (dd, *J* = 13.5, 11.0 Hz, 1H, C**H$_2$**-C2).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 168.9 (**C**O), 149.6, 149.4, 148.5, 147.3 (4x**C**-OCH_3), 127.3 (**C1'**), 124.8 (**C6a**), 121.2 (**C10a**), 120.7, 111.8, 111.7, 111.7 (CH_{Ar}), 111.2 (**C10**), 58.7 (**C2**), 56.1, 56.0, 55.9, 55.9 (4xO**C**H_3), 53.7 (**C1**), 53.4 (**H5**), 40.6 (SO_2**C**H_3), 38.1 (C**H$_2$**-C2), 31.0, 30.9 (**C6**).

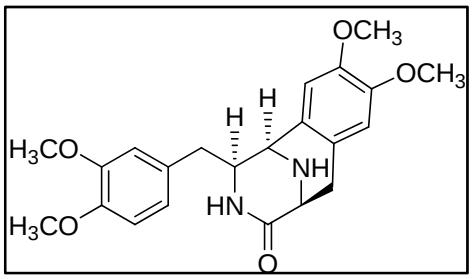
5.3.13.2. Synthesis of (±)-(1*R**, *2S**, *5S**) *tert*-butyl 8,9-dimethoxy-2-(3,4-dimethoxybenzyl)-4-oxo-2,3,5,6-tetrahydro-1,5-imino-1*H*-[3]benzazocin-11-carboxylate 26b.



According to the general procedure **5.3.13** using compound **24a** (1.00 g, 2.0 mmol) as starting material Pd/C (0.58 g), and EtOH (100 mL) as solvent for 3 h. The compound **26b** (0.99 g, 2.0 mmol) was obtained as a white solid in 99% yield as a mixture of amide rotamers in $CDCl_3$, 25 ºC. **Mp** 100–101 ºC; **IR (NaCl) ν_{max}** 3210,

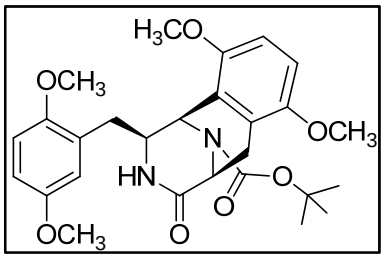
2930, 1693, 1625 cm^{-1}. **Analysis**: Calcd. for $C_{27}H_{34}O_7N_2$: C, 65.04; H, 6.87; N, 5.62. Found: C, 65.01; H, 6.78; N, 5.69.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.75 (m, 1H, C**H$_{Ar}$**), 6.64 – 6.59 (m, 3H, C**H$_{Ar}$**), 6.50 (s, 0.9H, **H10**), 6.49 (s, 0.1H, **H10**), 5.59 (s, 1H, N**H**), 5.28 (d, *J* = 3.5 Hz, 1H, **H1**), 4.79 (d, *J* = 6.1 Hz, 1H, **H5**), 4.15 – 4.06 (m, 1H, **H2**), 3.81 – 3.79 (m, 12H, 4xOC**H$_3$**), 3.14 (dd, *J* = 16.5, 6.6 Hz, 1H, **H6**), 3.04 – 2.98 (m, 1H, C**H$_2$**-C2), 2.94 – 2.77 (m, 1H, C**H$_2$**-C2), 2.18 (dd, *J* = 16.0, 9.3 Hz, 1H, **H6**), 1.44 (s, 3H, OC(C**H$_3$**)$_3$), 1.41 (s, 6H, OC(C**H$_3$**)$_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 170.2 (**C4**), 152.8 (**C**OOC(CH$_3$)$_3$), 149.4, 148.8, 148.2, 146.8 (4x**C**-OCH$_3$), 127.8 (**C1'**), 125.8, 122.0 (**C10a, C6a**), 121.1, 111.7, 111.6, 111.5 (**C**H$_{Ar}$), 81.1 (O**C**(CH$_3$)$_3$), 57.7 (**C5**), 56.0, 55.9, 55.8, 55.7 (4xO**C**H$_3$), 52.9 (**C2**), 51.2 (**C1**), 38.1 (**C**H$_2$-C2), 31.8 (**C6**), 28.2 (OC(**C**H$_3$)$_3$).

5.3.13.3. Synthesis of (1*R**, 2*S**, 5*S**)-8,9-dimethoxy-2-(3,4-dimethoxybenzyl)-2,3,5,6-tetrahydro-1,5-imino-[3]benzazocin-4(1*H*)-one 26c.



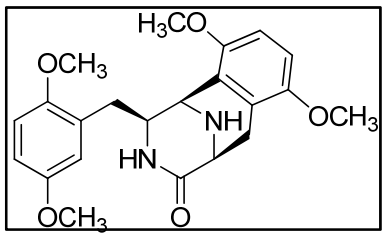
According to the general procedure **5.3.13** using compound **24b** (1.00 g, 2.5 mmol), C/Pd (0.58 g), as starting material and EtOH (100 mL) as solvent for 3 h. The compound **26c** (0.99 g, 2.5 mmol) was obtained as a white solid in 99% yield.; Mp 98-99 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}. **Analysis**: Calcd. for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03; Found: C, 66.30; H, 6.52; N, 7.09.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.85 (d, *J* = 8.1 Hz, 1H, **H6'**), 6.80 (dd, *J* = 8.1, 1.8 Hz, 1H, **H5'**), 6.76 (d, *J* = 1.5 Hz, 1H, **H2'**), 6.66 (d, *J* = 7.7 Hz, 1H, N**H**-C1), 6.56 (s, 1H, **H7**), 6.43 (s, 1H, **H10**), 5.84 (d, *J* = 2.9 Hz, 1H, **H3**), 3.94 (s, 1H, **H1**), 3.91 (dd, *J* = 6.6, 1.3 Hz, **H5**), 3.88 (s, 3H, OC**H$_3$**), 3.88 (s, 3H, OC**H$_3$**), 3.83 (s, 3H, OC**H$_3$**), 3.82 (s, 3H, OC**H$_3$**), 3.56 (td, *J* = 7.0, 3.1 Hz, 1H, **H2**), 3.12 – 3.05 (m, 1H, **H6**), 3.05 (d, *J* = 7.1 Hz, 2H, C**H$_2$**-C2), 2.92 (d, *J* = 16.4 Hz, 1H, **H6**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 172.3 (**C4**), 149.3, 148.6, 148.1, 147.8 (4x**C**-OCH$_3$), 129.8 (**C1'**), 128.8 (**C10a**), 125.2 (**C6a**), 121.4 (**C4**), 112.3 (**C2'**), 111.7, 111.7 (**C6', C7**), 109.2 (**C10**), 61.6 (**C2**), 56.2, 56.1, 56.0, 56.0 (4xO**C**H$_3$), 53.3 (**C5**), 52.0 (**C1**), 41.8 (**C**H$_2$-C2), 32.4 (**C6**).

5.3.13.4. Synthesis of (±)-(1*R**, 2*S**, 5*S**) *tert*-butyl 7,10-dimethoxy-2-(2,5-dimethoxybenzyl)-4-oxo-2,3,5,6-tetrahydro-1,5-imino-1*H*-[3]benzazocin-11-carboxylate 26d.



According to the general procedure **5.3.13** using compound **24d** (1.00 g, 2.0 mmol) as starting material, Pd/C (0.58 g), and EtOH (100 mL) as solvent for 3 h. The compound **26d** (0.99 g, 2.0 mmol) was obtained as a white solid in 99% yield as mixture of rotamers in $CDCl_3$, 25 ºC; **Mp** 184–185ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis:** Calcd. for $C_{27}H_{34}N_2O_7$: C, 65.04; H, 6.87; N, 5.62. Found: C, 65.00; H, 6.80; N, 5.59; **^{1}H NMR** δ 6.94 (d, *J* = 2.0 Hz, 0.6H, **H6'**), 6.83 (d, *J* = 2.0 Hz, 0.4H, **H6'**), 6.79 – 6.45 (m, 5H, C**H**$_{Ar}$), 5.36 (d, *J* = 19.5 Hz, 1H, **H1**), 4.93 (dd, *J* = 33.9, 5.8 Hz, 1H, **H5'**), 3.75 – 3.66 (m, 10.6H, OC**H$_3$**, **H2**), 3.50 (s, 1.4H, OC**H$_3$**), 2.94 (m, 4H, C**H$_2$**-C2, **H6**), 1.62 – 1.33 (m, 9H, OC(C**H$_3$**)$_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 170.4, 170.2 (N**C**O), 153.5*, 153.3* **(C7)**, 151.8, 151.6, 151.3, 151.0 (**C3', C4',** C**C**OOC(CH$_3$)$_3$), 149.4*, 149.2* **(C10)**, 126.8, 126.5, 125.8, 124.7, 124.6, 123.4, 122.8 (**C6a, C10a, C1'**), 118.0, 117.6, 117.2 (**C6'**), 112.6, 112.4, 111.4 (**C**H$_{Ar}$), 111.2, 110.8, 110.7 (**C**H$_{Ar}$), 108.9, 108.4, 108.2 (**C**H$_{Ar}$), 107.7, 107.6, 107.5 (**C**H$_{Ar}$), 80.7, 80.6, 80.4 (O**C**(CH$_3$)$_3$), 57.0, 56.9, 56.8, 55.6, 55.5, 55.4, 55.3, 55.0 (4xO**C**H$_3$, **C2**), 52.4, 50.8 (**C5**), 48.9, 45.8 (**C1**), 36.6 (**C**H$_2$-C2), 28.2 (OC(**C**H$_3$)$_3$), 26.5 (**C6**).

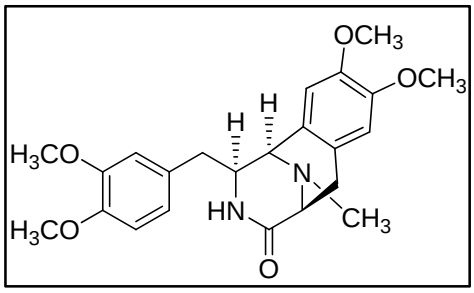
5.3.13.5. Synthesis of (±)-(1*R**, 2*S**, 5*S**) 7,10-dimethoxy-2-(2,5-dimethoxybenzyl)-2,3,5,6-tetrahydro-1,5-imino-[3]benzazocin-4(1*H*)-one 26e.



According to the general procedure **5.3.13** using compound **24e** (1.00 g, 2.5 mmol) as starting material, Pd/C (0.58 g), and EtOH (100 mL) as solvent for 3 h. The compound **26e** (0.99 g, 2.5 mmol) was obtained as a white solid in 99% yield; **Mp** 99–100 ºC; **IR (NaCl) ν_{max}** 2938, 1677, 1514, 1488, 1456 cm^{-1}; **Analysis: Calcd.** for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03 Found: C, 66.16; H, 6.38 ; N, 7.00.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.85 – 6.70 (m, 3H, **H3', H4', H6'**), 6.59 (m, 2H, **H8, H9**), 6.11 (bs, 1H, **H3**), 4.19 (s, 1H, **H1**), 3.89 (d, *J* = 6.4 Hz, 2H, **H5**), 3.77 (s, 3H, C2'-OC**H$_3$**), 3.75 (s, 3H, C5'-OC**H$_3$**), 3.71 (s, 3H, C7-OC**H$_3$**), 3.68 – 3.64 (m, 1H, **H2**), 3.55 (s, 3H, C10-OC**H$_3$**), 3.18-3.06 (m, 1H, C**H$_2$** -C2), 3.06 – 3.02 (m, 1H, **H6**), 2.97 – 2.89 (m, 1H, C**H$_2$** -C2), 2.89 – 2.61 (m, 1H, **H6**), 2.58 (bs, 1H,

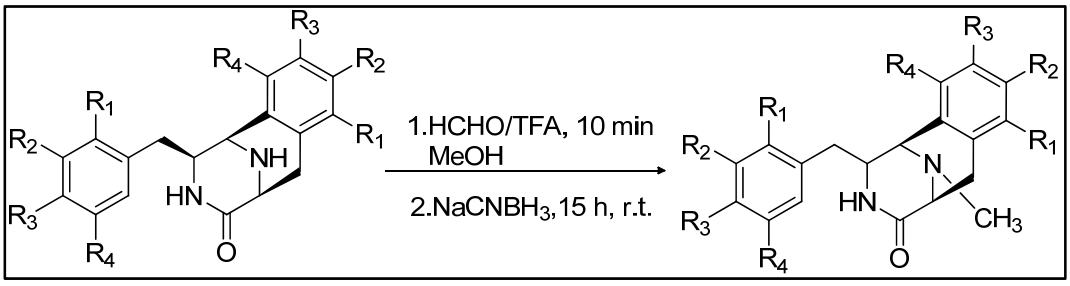
H11).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 172.8 (**C4**), 153.5 (**C5'**), 152.0 (**C2'**), 151.4 (**C7**), 149.5 (**C10**), 127.1, 126.8 (**C10a, C1'**), 123.6 (**C6a**), 117.5 (**C6'**), 112.1, 111.2 (**C3', C4'**), 108.1, 107.5 (**C8, C9**), 57.6 (**C2**), 55.9, 55.8, 55.6, 55.2 (4xOCH_3), 52.3 (**C5**), 46.5 (**C1**), 36.4 (CH_2-C2), 27.8 (**C6**).

5.3.13.6. (1*R**, 2*S**, 5*S**)-8,9-dimethoxy-2-(3,4-dimethoxybenzyl)-11-methyl-2,3,5,6-tetrahydro-1,5-imino[3]benzazocin-4(1*H*)-one 27a.



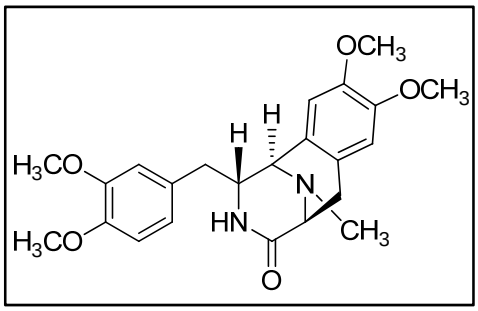
Obtained according to the general procedure **5.3.13** using compound **25a** (1.0 g, 2.51 mmol) as starting material, HCHO (0.6 mL, 8.03 mmol), $NaCNBH_3$ (0.31 g, 5.02 mmol), TFA (0.30 mL, 4.05 mmol) and MeOH (15 mL) as solvent for 64 h. Purification by flash column chromatography on silica gel using 7:3 ethyl acetate:methanol as eluent afforded product **27a** (0.38 g, 0.93 mmol) as a pale yellow solid in 99% yield; **Mp** 103 – 104 ºC; **IR (NaCl) ν_{max}** 3220, 2930, 1693cm^{-1}; **Analysis**: Calcd. for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.90; H, 6.70; N, 6.83.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.78 (d, *J* = 7.9 Hz, 1H, **H5**'), 6.68 – 6.60 (m, 3H, C**H$_{Ar}$**), 6.54 (s, 1H, **H10**), 5.45 (s, 1H, N**H**), 4.20 (dt, *J* = 11.3, 3.4 Hz, 1H, **H2**), 3.87 (s, 3H, OC**H$_3$**), 3.84 (s, 3H, OC**H$_3$**), 3.83 (s, 6H, OC**H$_3$**), 3.84 – 3.81 (m, 1H, **H1**), 3.60 (d, *J* = 6.7 Hz, 1H, **H5**), 3.21 (dd, *J* = 17.3, 6.8 Hz, 1H, **H6**), 2.95 (dd, *J* = 13.5, 2.8 Hz, 1H, C**H$_2$**-C2), 2.80 (d, *J* = 17.4 Hz, 1H, **H6**), 2.49 (s, 3H, NC**H$_3$**), 2.11 (dd, *J* = 13.1, 11.5 Hz, 1H, C**H$_2$**-C2).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 172.4 (**C4**), 149.5, 148.8, 148.4, 147.0 (4x**C**-OCH_3), 128.5, 125.6, 121.9 (**C10a, C6a, C1'**), 121.2 (CH_{Ar}), 112.5 (**C10**), 112.0, 111.8, 111.5 (CH_{Ar}), 59.8 (**C1**), 59.2 (**C5**), 56.9 (**C2**), 56.2, 56.1, 56.0, 55.9 (4xO**C**H_3), 40.0 (N**C**H_3), 38.7 (CH_2-C2), 27.2 (**C6**).

5.3.14. General procedure to obtain 2-alcoxybenzyl-11-methyl-1,5-imino-[3]benzazocins 28a–28b.



To a solution of **26c** or **26e** (1.0 eq) in methanol (3.0 - 9.0 mL), formaldehyde 37% (3.2 - 1.6 eq) and TFA (1.6 eq) was added. The reaction was stirred for 10 min. Then, sodium cianoborohydride (2.0 eq) was added and the reaction was stirred at room temperature for 15 – 48 h. The mixture was quenched with a saturated solution of $NaHCO_3$ and extracted with DCM (3x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography using a mixture of ethyl acetate:methanol as eluent to obtain **28a – 28b.**

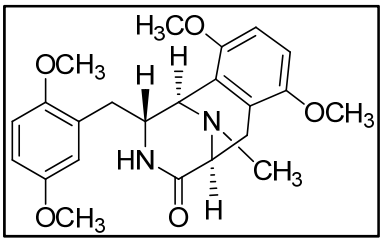
5.3.14.1. (1*R**, 2*R** 5*S**)-8,9-dimethoxy-2-(3,4-dimethoxybenzyl)-11-methyl-2,3,5,6-tetrahydro-1,5-imino[3]benzazocin-4(1*H*)-one 28a.



Obtained according to the general procedure **5.3.14** using compound **26c** (0.6 g, 1.51 mmol) as a starting material, formaldehyde 37% (0.18 mL, 2.41 mmol), TFA (0.18 mL), $NaCNBH_3$ (0.19 g, 3.0 mmol) and methanol (9.0 mL) as solvent for 15h. Purification by flash column chromatography on silica gel using 9:1 ethyl acetate:methanol as eluent afforded product **28a** (0.36 g, 0.88 mmol) as a pale yellow solid in 58% yield; **Mp** 59–60 ºC; **IR (NaCl)** ν_{max} 3220, 2930, 1693 cm^{-1}. **Analysis**: Calcd**.** for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.88; H, 6.82; N, 6.66.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.0 Hz, 1H, **H5'**), 6.76 (d, *J* = 1.6 Hz, 1H, **H2'**), 6.72 (s, 1H, **H6'**), 6.64 (s, 1H, N**H**), 6.47 (s, 1H, **H7**), 6.26 (s, 1H, **H10**), 3.83 (s, 3H, OC**H$_3$**), 3.82 (s, 3H, OC**H$_3$**), 3.75 (s, 3H, OC**H$_3$**), 3.72 (s, 3H, OC**H$_3$**), 3.60 (d, *J* = 6.7 Hz, 1H, **H5**), 3.41 (d, *J* = 6.8 Hz, 1H, **H1**), 3.39 – 3.31 (m, 1H, **H2**), 3.10 (dd, *J* = 17.3, 6.4 Hz, 1H, **H6**), 3.00 (d, *J* = 7.4 Hz, 2H, C**H$_2$**-C2), 2.60 (d, *J* = 17.3 Hz, 1H, **H6**), 2.36 (s, 3H, NC**H$_3$**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 172.7 (**C4**), 149.1, 148.3, 147.9, 147.7 (4x**C**-OCH_3), 130.6 (**C1'**), 125.7 (**C10a**), 124.4 (**C6a**), 121.3 (**C6'**),

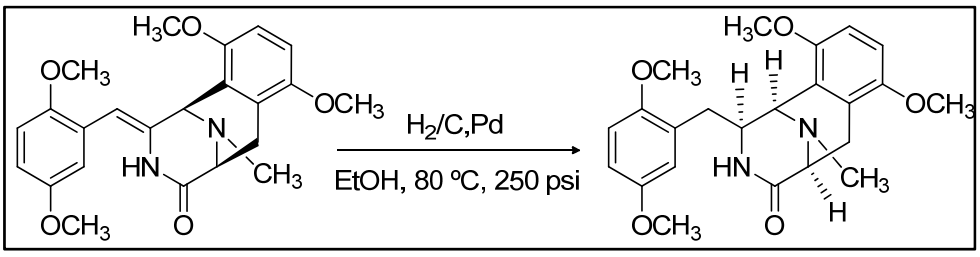
112.3 (**C5'**), 111.5, 111.2 (***C7, *C2'**), 110.1 (**C10**), 61.5 (**C2**), 59.2 (**C5**), 57.4 (**C1**), 55.9, 55.8, 55.7 (4xO**C**H_3), 41.2 (**C**H_2-C2), 39.4 (N**C**H_3), 24.1 (**C6**).

5.3.14.2. (*1R*,2R*,5S**)-7,10-dimethoxy-2-(2,5-dimethoxybenzyl)-2,3,5,6-tetrahydro-1,5-imino[3]benzazocin-4(1*H*)-one 28b.



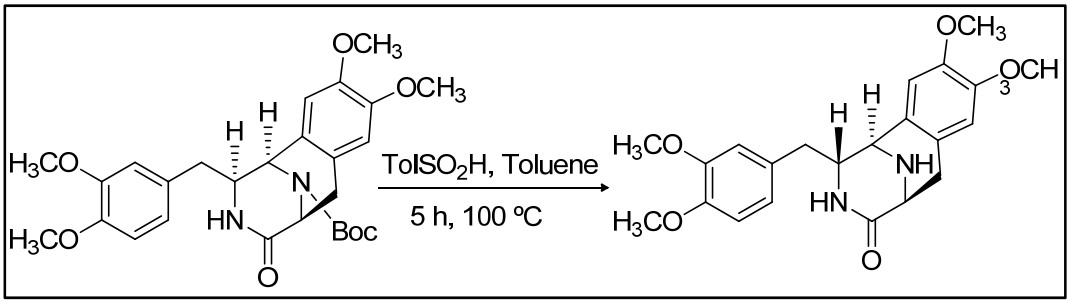
Obtained according to the general procedure **5.3.14** using compound **26e** (0.2 g, 0.5 mmol) as starting material, HCHO (1.2 mL, 16.06 mmol), $NaCNBH_3$ (0.31 g, 5.02 mmol), TFA (0.06 mL, 0.80 mmol) and MeOH (3 mL) as solvent, for 48 h. Purification by flash column chromatography on silica gel using 7:3 ethyl acetate:methanol as eluent afforded product **28b** (0.11 g, 0.27 mmol) as a brown solid in 53% yield.; **Mp** 90–91 ºC; **IR (NaCl) ν_{max}** 3205, 2930, 1680, 1620 cm^{-1}; **Analysis**: Calcd. for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.35; H, 6.51; N, 6.97; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.83 – 6.72* (m, 3H, **H3', H4', H6', H9**), 6.60 – 6.59* (m, 1H, **H8**), 5.72 (d, *J* = 2.7 Hz, 1H, N**H**), 3.88 (s, 1H, **H1**), 3.77 (s, 3H, O**C**$\mathbf{H_3}$), 3.76 (s, 3H, O**C**$\mathbf{H_3}$), 3.73 (s, 3H, O**C**$\mathbf{H_3}$), 3.71 – 3.67 (m, 1H, **H5**), 3.61-3.53 (m, 4H, O**C**$\mathbf{H_3}$**, H1**), 3.17 (dd, *J* = 12.8, 7.4 Hz, 1H, **H6**), 2.98 (dd, *J* = 12.8, 6.7 Hz, 1H, **H6**), 2.92 (dd, *J* = 20.9, 6.6 Hz, 1H, C$\mathbf{H_2}$-C2), 2.76 (dd, *J* = 20.0, 1.9 Hz, 1H, C$\mathbf{H_2}$-C2), 2.39 (s, 3H, N-C$\mathbf{H_3}$).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 172.7 (N**C**O), 153.5, 152.2 (**C5', C7**), 150.8, 150.7 (**C2', C10**), 127.8 (**C1'**), 123.5, 122.8 (**C6a, C10a**), 117.8 (**C6'**), 111.9, 111.2, 107.8, 107.4 (**C3', C4', C8, C9**), 58.6 (**C5**), 57.4 (**C2**), 55.8, 55.7, 55.6, 55.1 (4xO**C**H_3), 53.0 (**C1**), 39.6 (N-C$\mathbf{H_3}$), 37.0 (**C6**), 19.5 (**C**H_2-C2).

5.3.15. (*1R*,2S*,5S**)-7,10-dimethoxy-2-(2,5-dimethoxybenzyl)-2,3,5,6-tetrahydro-1,5-imino[3]benzazocin-4(1*H*)-one 27b.



To a solution of **25b** or **25c** (0.076 g, 0.19 mmol.) in ethanol (3 mL) under an Ar atmosphere was added 10% Pd/C (52 % w/w). The reaction was carried out under hydrogen (200 psi) and stirred for 4 h at 80 ºC. The reaction was filtered through celite to remove the Pd/C, which was washed with DCM (3x 30 mL) to recover completely the compound from the celite and the organic layer was washed with saturated aqueous solution of $NaHSO_3$ (25 mL). The solution was extracted with DCM (2x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. to obtain **27b** (0.078 g, 0.19 mmol) as a white solid in 99% yield; **Mp** 90–91ºC; **IR (NaCl) ν_{max}** 3205, 2931, 1690, 1614 cm^{-1}; **Analysis**: Calcd. for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.29; H, 6.47; N, 7.05; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.73 (m, 4H, **H8, H9, H3', H4'**), 6.52 (d, *J* = 2.6 Hz, 1H, **H6'**), 5.48 (s, 1H, N**H**), 4.38 (dd, *J* = 10.2, 3.4 Hz, 1H, **H1**), 4.32 (m, 1H, **H2**), 3.79 (s, 3H, OC**H$_3$**), 3.77 (s, 3H, OC**H$_3$**), 3.76 (s, 3H, OC**H$_3$**), 3.69 (s, 3H, OC**H$_3$**), 3.65 – 3.57 (m, 1H, **H5**), 3.38 (dd, *J* = 13.5, 2.4 Hz, 1H, C**H$_2$**-C2), 2.94 (m, 2H, **H6**), 2.45 (s, 3H, N-C**H$_3$**), 1.88 (t, *J* = 12.5 Hz, 1H, C**H$_2$**-C2); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 172.4 (N**C**O), 153.6 (**C5'**), 152.0 (**C2'**), 151.4, 151.3 (**C7, C10**), 126.3 (**C1'**), 123.8, 120.8 (**C6a, C10a**), 117.6 (**C6'**), 112.7, 111.5, 108.6, 107.4 (**C3', C4', C8, *C9**), 58.2 (**C5**), 56.0, 55.8, 55.7, 55.6, 55.3 (4xO**C**H$_3$, **C2**), 53.8 (**C1**), 40.2 (N-**C**H$_3$), 33.3 (**C**H$_2$-C2), 23.4 (**C6**).

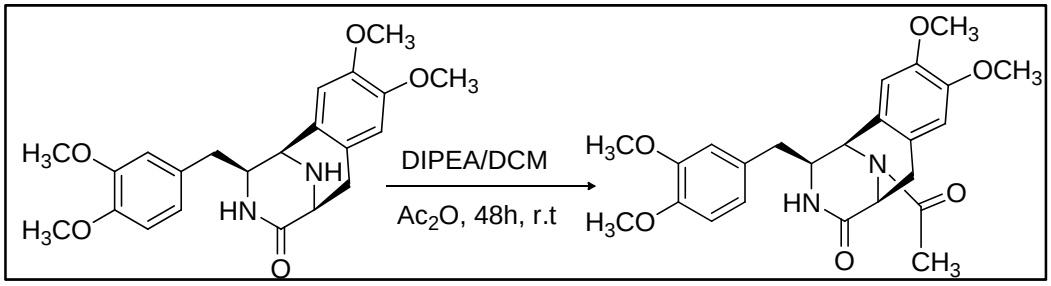
5.3.16. Synthesis of (1*R**, 2*S**, 5*S**)-8,9-dimethoxy-2-(3,4-dimethoxybenzyl)-2,3,5,6-tetrahydro-1,5-imino[3]benzazocin-4(1*H*)-one 29.



To a solution of **26b** (0.1 g, 0.2mmol) in toluene (0.5 mL), *p*-toluene sulfinic acid (0.05 g, 0.3 mmol) and benzaldehyde (0.025 g, 0.24mmol) were added. The reaction was stirred and heated at 100 ºC for 5 h. Then was quenched with a saturated solution of $NaHCO_3$ and extracted with DCM (2x 20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash column chromatography using a mixture of 9.1 ethyl acetate:methanol as eluent to obtain **29** (0.04 g, 0.1 mmol) as a white solid in 50% yield.; **Mp** 90-91 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03; O, 20.08. Found: C, 66.30; H, 6.52; N, 7.09.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.79 (d, *J* = 7.9 Hz, 1H, **H5'**), 6.66* (dd, *J* = 8.1, 2.0

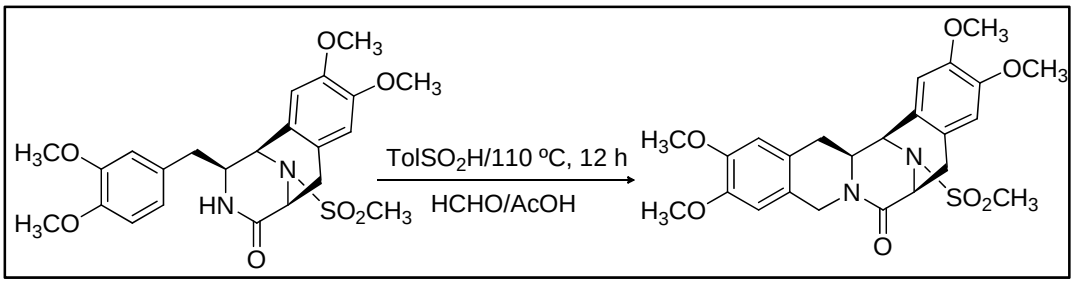
Hz, 3H, **H10, H6', H2'**), 6.55* (s, 1H, **H7**), 5.47 (s, 1H, **H3**), 4.17 (bs, 1H, **H1**), 4.15 – 4.03 (m, 1H, **H5**), 3.93 (d, *J* = 5.9 Hz, 1H, **H2**), 3.87 (s, 3H, O**CH$_3$**), 3.85 (s, 6H, O**CH$_3$**), 3.84 (s, 3H, O**CH$_3$**), 3.15 (dd, *J* = 17.0, 6.0 Hz, 1H, C**H$_2$**-C2), 3.08 – 2.93 (m, 2H, C**H$_2$**-C2, **H6**), 2.60 (bs, 1H, N**H**), 2.15 (t, *J* = 12.4 Hz, 1H, **H6**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 172.2 (**C4**), 149.5, 148.9, 148.3, 146.8 (4x**C**-OCH_3), 128.3, 126.3, 124.0 (**C1', C6a, C10a**), 121.2, 112.0, 111.8, 111.7, 111.6 (**C**H_{Ar}), 59.6 (**C2**), 56.2, 56.1, 56.0, 56.0 (4xO**C**H_3), 53.1, 53.1 (**C1, C5**), 38.9 (**C**H_2-C2), 32.8 (**C6**).

5.3.17. Synthesis of (1*R**, 2*S**, 5*S**)-11-acetyl-8,9-dimethoxy-2-(3,4-dimethoxybenzyl)-2,3,5,6-tetrahydro-1,5-imino[3]benzazocin-4(1*H*)-one 30.



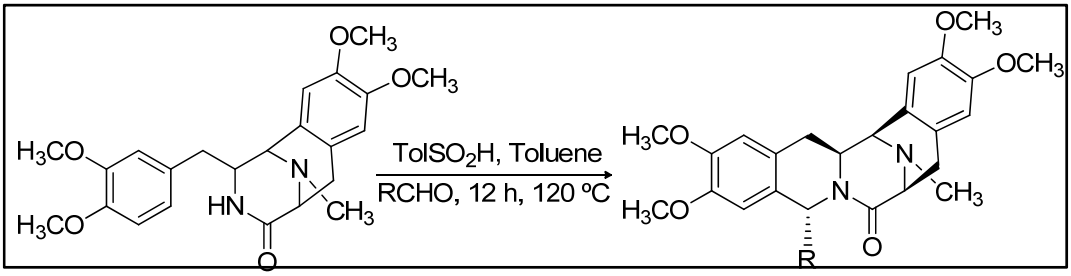
To a solution of **26c** (0.51 g, 1.29 mmol) in DCM (3.0 mL) DIPEA (0.48 mL, 2.80 mmol) was added. The mixture was stirred for 10 min then acetic anhydride (0.36 mL, 3.87 mmol) was added. The reaction was stirred at room temperature for 48 h. The mixture was quenched with a saturate solution of $NaHCO_3$, extracted with DCM (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The compound **29** (0.48 g, 1.1 mmol) was obtained as a yellow solid in 85% yield; **Mp** 97–98ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1790 cm^{-1}; **Analysis:** Calcd. for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.37; H, 6.40; N, 6.50. **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.84 – 6.77* (m, 2H, **H5', H6'**), 6.64 – 6.50 (m, 3H, **H7, H10, H2'**), 5.83 (d, *J* = 3.8 Hz, 1H, **H1**), 5.55 (s, 1H, N**H**), 4.63 (d, *J* = 5.2 Hz, 1H, **H5**), 4.07 (dt, *J* = 11.7, 3.8 Hz, 1H, **H2**), 3.87 (d, *J* = 4.3 Hz, 82H), 3.20 – 3.18 (m, 2H, **H6**), 3.14 – 3.07 (m, 1H, C**H$_2$**-C2), 2.26 – 2.19 (m, 1H, C**H$_2$**-C2), 2.16 (s, 0.6H, CO**CH$_3$**), 2.15 (s, 2.4H, CO**CH$_3$**). **^{13}C NMR** (63 MHz, $CDCl_3$) δ 169.3 (**C4**), 167.5 (**C**OCH_3), 149.7, 149.2, 148.6, 147.4 (4x**C**-OCH_3), 127.7, 125.3, 121.9 (**C1', C6a, C10a**), 121.3, 111.9, 111.8, 111.7, 111.6 (**C2', C5', C6', C7', C10'**), 57.5 (**C2**), 56.2, 56.1, 56.1, 56.0 (4xO**C**H_3), 55.2 (**H5**), 49.6 (**H1**), 38.3 (**C**H_2-C2), 32.9 (**C6**), 20.8 (CO**C**H_3).

5.3.18. Synthesis of (1*R**, 2*S**, 5*S**)-11-ethyl-8,9-dimethoxy-2-(3,4-dimethoxybenzyl)-2,3,5,6-tetrahydro-1,5-imino[3]benzazocin-4(1*H*)-one 31a.



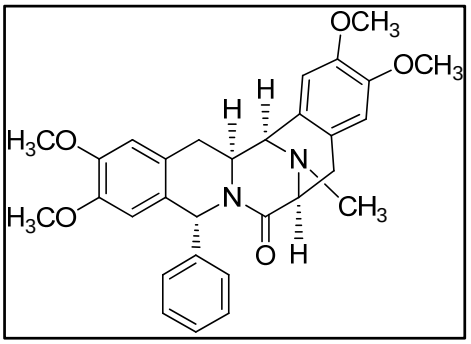
To a solution of **26a** (0.1 g, 0.18 mmol) in acetic acid (1.0 mL) *p*-toluenesulfinic acid (0.085 g, 0.54 mmol) and formaldehyde (4.0 mL) were added and the reaction was stirred at 110 ºC for 12 h. The reaction was quenched with saturated solution of $NaHCO_3$, extracted with DCM (2x 20 mL), and the organic layer was dried over anhydrous Na_2SO_4 and filtered. The solution was concentrated *in vacuo* and purified by flash column chromatography using a mixture of 7:3 ethyl acetate:methanol as eluent to obtain **31a** (0.020 g, 0.041 mmol) as a pale yellow solid in 23% yield; **Mp** 101–102 ºC; **IR (NaCl)** ν_{max} 2930, 1790 cm^{-1}; **Analysis:** Calcd. for $C_{24}H_{28}N_2SO_7$: C, 59.00; H, 5.78; N, 5.73; S, 6.56. Found: C, 59.10; H, 5.80; N, 5.69; S, 6.50; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.62 (m, 5H, C**H**$_{Ar}$), 4.63 (d, *J* = 17.6 Hz, 1H, **H9**), 4.49 (d, *J* = 17.6 Hz, 1H, **H9**), 4.14 – 4.07 (m, 1H, **H14a**), 3.91 – 3.83 (m, 13H, 4xOC**H$_3$**, **H15**), 3.75 (d, *J* = 6.8 Hz, 1H, **H6**), 3.22 (dd, *J* = 17.3, 6.8 Hz, 1H, **H14**), 2.88 (d, *J* = 17.3 Hz, 1H, **H14**), 2.71 (dd, *J* = 14.4, 2.5 Hz, 1H, **H5**), 2.49 (s, 3H, SO_2C**H$_3$**), 2.39 (d, *J* = 14.0 Hz, 1H, **H5**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 170.8 (N**C**O), 149.0, 148.1, 147.8, 147.1 (4x**C**-OCH$_3$), 125.8, 125.7, 123.5, 122.3 (**C4a, C9a, C13a, C15a**), 112.9, 111.6, 110.8, 109.4 (**C**H$_{Ar}$), 60.2 (**C15**), 59.6 (**C6**), 56.4, 56.4, 56.1, 56.1, 56.0 (**C14a,** 4xO**C**H$_3$), 44.6 (**C9**), 40.0 (SO_2**C**H$_3$), 33.5 (**C5**), 27.4 (**C14**).

5.3.19. General procedure to obtain (6*S**, 9RS*, 14a*S**, 15*R**)-9-(aryl)-2,3,11,12-tetramethoxy-16-methyl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 31b.



To a solution of **27a** (1.0 eq) in toluene (1.0 mL) *p*-toluene sulfinic acid (3.0 eq) and the corresponded aldehyde (2.0–4.0 eq) were added. The reaction was stirred and heated to 120 ºC for 12 h. The crude was quenched with a saturated solution of $NaHCO_3$, extracted with DCM (2 x 20 mL) and the organic layer was dried over anhydrous Na_2SO_4 and filtered. The solution was concentrated *in vacuo* and purified by flash column chromatography using a mixture of 1.1 ethyl acetate:ethyl ether as eluent to obtain **31b-31c**.

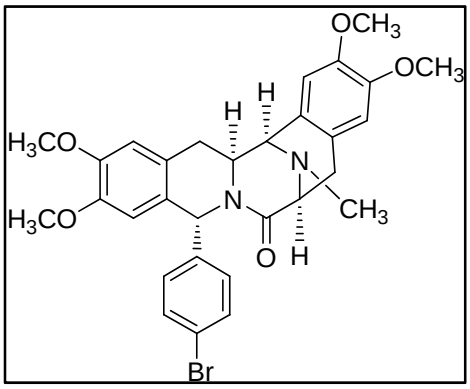
5.3.19.1. Synthesis of (6*S**, 9R* o S*, 14a*S**, 15*R**)-2,3,11,12-tetramethoxy-16-methyl-9-phenyl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 31b.



Obtained according to the general procedure **5.3.19** using compound **27a** (0.05 g, 0.12 mmol) as starting material, benzaldehyde (0.10 g, 0.96 mmol), *p*-toluenesulfinic acid (0.056 g, 0.36 mmol) and toluene (1.0 mL) as solvent. Purification by flash column chromatography on silica gel using 1:1 ethyl acetate: ethyl ether as eluent afforded product **31b** (0.012 g, 0.024 mmol) as a pale yellow oil in 20% yield. **IR (NaCl)** ν_{max} 3200, 2930, 1693, 1625 cm^{-1};

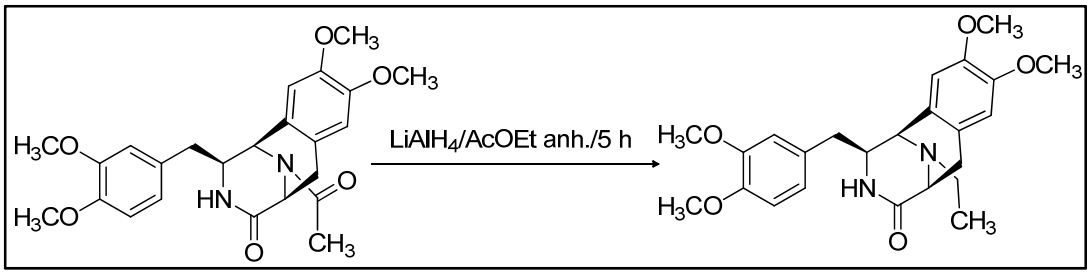
Analysis: Calcd. for $C_{30}H_{32}N_2O_5$: C, 71.98; H, 6.44; N, 5.60. Found: C, 71.94; H, 6.45; N, 5.59. **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 4H, **H2', H3', H5', H6'**), 7.21 – 7.19 (m, 2H, **H10, H13**), 6.97 (d, *J* = 5.8 Hz, 1H, **H4'**), 6.89 (s, 1H, **H9**), 6.66* (s, 1H, **H1**), 6.45* (s, 1H, **H4**), 4.36 – 4.19** (m, 2H, **H14a, H15**), 4.16 – 4.03** (m, 1H, **H6**), 4.00 – 3.80 (m, 6H, 2xOC**H$_3$**), 3.72 (d, *J* = 6.2 Hz, 6H, 2xOC**H$_3$**), 3.50$^{\#}$ (m, 2H, **H5**), 3.04 – 2.93$^{\#}$ (m, 2H, **H14**), 2.17 (s, 3H).**^{13}C NMR** (63 MHz, $CDCl_3$) δ 163.70 (**C**O), 148.65, 148.32, 148.20, 147.85 (4x**C**-OCH_3), 141.49 (**C1'**), 129.46* (**C10**), 128.80, 128.78 (**C2', C3', C6', C5'**), 128.44** (**C13a**), 128.38* (**C13**), 128.17** (**C9a**), 125.67 (**C4'**), 124.85, 124.45 (**C15a, C4a**), 111.09, 110.87 (**C1, C4**), 56.11, 56.06 (4xO**C**H_3), 56.01$^{\#}$ (**C5**), 54.99 (**C9**), 51.72, 51.13$^{\#}$ (**C14a, C15**), 34.56 (**C14**), 30.45 (N-**C**H_3), 29.84 (**C5**).

5.3.19.2. Synthesis of (6*S*, 9R* o S*, 14a*S*, 15*R*)-9-(4-bromophenyl)-2,3,11,12-tetramethoxy-16-methyl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 31c.



Obtained according to the general procedure **5.3.19** using compound **27a** (0.05 g, 0.12 mmol) as starting material, *p*-bromobenzaldehyde (0.044 g, 0.24 mmol), *p*-toluenesulfinic acid (0.056 g, 0.36 mmol) and toluene (1.0 mL) as solvent. Purification by flash column chromatography on silica gel using 1:1 ethyl acetate: ethyl ether as eluent afforded product **31c** (0.016 g, 0.028 mmol) as a pale yellow oil in 23% yield. **IR (NaCl) ν_{max}** 3200, 2910, 1693, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{30}H_{31}BrN_2O_5$: C, 62.18; H, 5.39; N, 4.83; Found: C, 62.14; H, 5.43; N, 4.80. **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.45* (d, *J* = 8.4 Hz, 2H, **H2', H3'**), 7.25* (d, *J* = 8.4 Hz, 2H, **H5', H6'**), 6.64 – 6.56 (m, 4H, **H1, H4, H10, H13**), 6.29 (s, 1H, **H9**), 4.40** (dd, *J* = 6.7, 4.1 Hz, 1H, **H15**), 3.99 – 3.86** (m, 11H, 3xOC**H$_3$**, **H5, H14a**), 3.69 (s, 3H. OC**H$_3$**), 2.99 – 2.72 (m, 2H, **H5*, H14***), 2.61 – 2.46 (m, 2H, **H5, H14**), 2.34 (s, 3H, C**H$_3$**).

5.3.20. Synthesis of (1*R**, 2*S**, 5*S**)-11-ethyl-8,9-dimethoxy-2-(3,4-dimethoxybenzyl)-2,3,5,6-tetrahydro-1,5-imino[3]benzazocin-4(1*H*)-one 32.

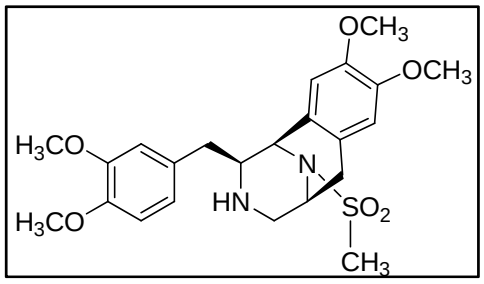


A solution of $LiAlH_4$ (0.056 mg, 1.47 mmol) in dry ethyl acetate (0.29 mL, 2.94 mmol) was stirred for 2 h at 0 ºC. Then, compound **30** (0.11 g, 0.23 mmol) was added and left stirred for 5 h at room temperature. The mixture was quenched with a saturate solution of $NaHCO_3$, extracted with DCM (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography using a mixture of 95:5 ethyl acetate:methanol as eluent to obtain **32** (0.40 g, 0.094 mmol) as a pale yellow solid in 41% yield; **Mp** 90–91 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis:** Calcd. for $C_{24}H_{30}N_2O_5$: C, 67.59; H, 7.09; N, 6.57. Found: C, 67.50; H, 7.09; N, 6.59; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.80 (s, 1H, C**H**$_{Ar}$), 6.77 (s, 1H, C**H**$_{Ar}$), 6.67 (d, *J* = 1.8 Hz, 1H, C**H**$_{Ar}$), 6.64 (s, 1H, C**H**$_{Ar}$), 6.54 (s, 1H, **H7**), 5.49 (s, 1H, N**H**), 4.21 – 4.12 (m, 1H, **H2**), 3.94 (d, *J* = 4.2 Hz, 1H, **H1**), 3.87 (s, 3H, OC**H$_3$**), 3.85 (s, 6H, OC**H$_3$**), 3.84 (s, 3H, OC**H$_3$**), 3.74 (d, *J* = 6.1 Hz, 1H, **H5**), 3.16 (dd, *J* = 17.4, 6.9 Hz, 1H, **H6**), 2.97 (dd, *J* = 13.6, 3.2 Hz, 1H, C**H$_2$**-C2), 2.80 (d, *J* = 17.3 Hz, 1H, **H6**), 2.65 (q, *J* = 7.1 Hz, 2H, NC**H$_2$**CH$_3$), 2.13 (dd, *J* = 13.5, 11.6 Hz, 1H, C**H$_2$**-C2), 1.16 (t, *J* = 7.1 Hz, 3H, NCH$_2$C**H$_3$**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 172.6 (**C**O), 149.5, 148.8, 148.3, 147.0 (4x**C**-OCH$_3$), 128.6 (**C1'**), 126.0 (**C10a**), 122.3 (**C6a**), 121.3, 112.5, 112.1, 111.7, 111.6 (**C**H$_{Ar}$), 57.9 (**C1**), 57.2 (**C2**), 56.2, 56.1, 56.1, 56.0, 55.9 (**C5,** 4xO**C**H$_3$), 45.7 (N**C**H$_2$CH$_3$), 38.9 (**C**H$_2$-C2), 27.4 (**C6**), 13.0 (NCH$_2$**C**H$_3$).

5.3.21. General procedure for the reduction of the position 4 33a–33b.

A solution of $LiAlH_4$ (6.0 eq) in dry ethyl acetate (12.0 eq) and dry THF (1.0 mL) was stirred at 0 ºC for 2 h. Then, compounds **26a** or **26b** (1.0 eq.) were added and stirred for 5 h at room temperature. The mixture was quenched with a saturate solution of $NaHCO_3$, extracted with DCM (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography using a mixture of ethyl acetate:methanol as eluent to obtain **33**.

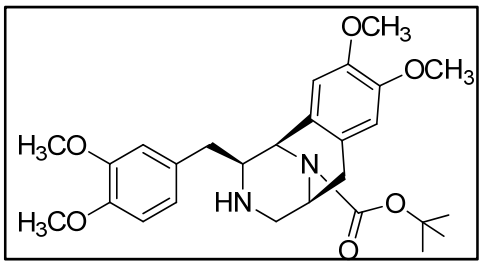
5.3.21.1. Synthesis of (1*R**, 2*S**, 5*S**)-8,9-dimethoxy-2-(3,4-dimethoxybenzyl)-11-(methylsulfonyl)-1,2,3,4,5,6-hexahydro-1,5-imino[3]benzazocin 33a.



Obtained according to the general procedure **5.3.21** using compound **26a** (0.1 g, 0.18 mmol) as starting material, $LiAlH_4$ (0.041 g, 1.08 mmol), AcOEt (0.21 mL, 2.16 mmol), and THF (1 mL) as solvents. Purification by flash column chromatography on silica gel using 95:5 ethyl acetate:methanol as eluent afforded product **33a** (0.044 g, 0.095 mmol) as a pale yellow solid in 53% yield; **Mp** 167–168ºC; **IR (NaCl)** ν_{max} 3100, 2920 cm^{-1}; **Analysis:** Calcd. for $C_{23}H_{30}N_2SO_6$: C, 59.72; H, 6.54; N, 6.06; S, 6.93. Found: C, 59.60; H, 6.70; N, 6.09; S, 7.00; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.6 Hz, 1H, **H5'**), 6.70 (s, 10H, **H6'**), 6.69 (s, 1H, **H7**), 6.68 – 6.66 (m, 1H, **H2'**), 6.50 (s, 1H, **H10**), 4.64 (d, *J* = 1.3 Hz, 1H, **H1**), 4.22 (d, *J* = 7.5 Hz, 1H, **H5**), 3.85 – 3.84 (m, 12H, 4xOC**H$_3$**), 3.44 – 3.37 (m, 1H, **H2**), 3.21 – 3.14 (m, 2H, **H4, H6**), 3.01 (dd, *J* = 12.0, 1.8 Hz, 1H, **H4**), 2.80 (d, *J* = 17.8 Hz, 1H, **H6**), 2.69 (dd, *J* = 13.9, 4.8 Hz, 1H, C**H$_2$**-C2), 2.50 (s, 3H, SO_2C**H$_3$**), 2.18 (dd, *J* = 13.9, 9.7 Hz, 1H, C**H$_2$**-C2); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 149.2, 148.8, 147.8, 146.8

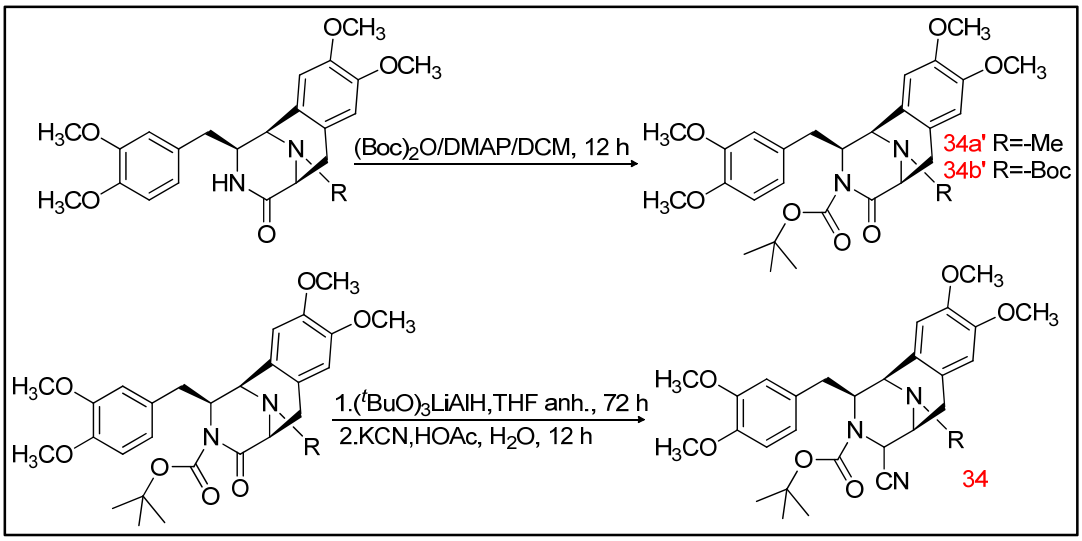
(4x**C**-OCH_3), 130.0 (**C1'**), 127.5 (**C6a**), 123.6 (**C10a**), 121.1 (**C6'**), 112.0 (**C2'**), 111.3, 111.2 (**C5', C7**), 110.9 (**C10a**), 60.7 (**C2**), 56.6 (**C1**), 56.2, 56.1, 56.0, 55.9 (4x**O**CH_3), 54.2 (**C4**), 48.3 (**C5**), 39.6 (SO_2**C**H_3), 39.1 (CH_2-C2), 30.4 (**C6**).

5.3.21.2. Synthesis of *tert*-butyl (1*R**, 2*S**, 5*S**)-8,9-dimethoxy-2-(3,4-dimethoxybenzyl)-1,2,3,4,5,6-hexahydro-1,5-imino[3]benzazocin-11-carboxylate 33b.



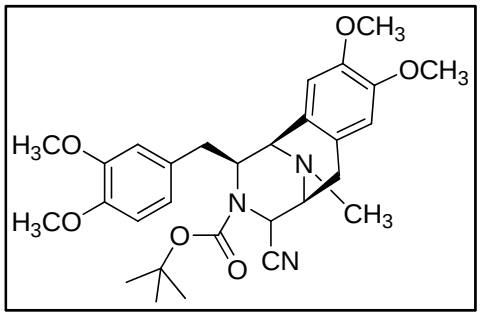
Obtained according to the general procedure **5.3.21** using compound **26b** (0.11 g, 0.23 mmol), $LiAlH_4$ (0.056 g, 1.38 mmol), AcOEt (0.29 mL, 2.76 mmol), as starting material and THF (1.0 mL) as solvent. Purification by flash column chromatography on silica gel using 95:5 ethyl acetate: methanol as eluent afforded product **33b** (0.085 g, 0.18 mmol) as a pale yellow solid in 76% yield as a mixture of rotamers in $CDCl_3$, 25 ºC; **Mp** 100 – 101 ºC; **IR (NaCl) ν_{max}** 3109, 2950, 1693 cm^{-1}; **Analysis**: Calcd. for $C_{27}H_{36}N_2O_6$: C, 66.92; H, 7.49; N, 5.78. Found: C, 66.90; H, 7.41; N, 5.69.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.87 – 6.35 (m, 5H, C**H$_{Ar}$**), 5.00 (s, 0.5H, **H1**), 4.78 (s, 0.5H, **H1**), 4.47 (bs, 0.5H, **H5**), 4.47 (bs, 0.5H, **H5**), 3.89 – 3.78 (m, 12H, 4xOC**H$_3$**), 3.40 – 3.14 (m, 2H, **H2, H6**), 3.06 – 2.87 (m, 2H, **H4**), 2.81 – 2.60 (m, 2H, **H6**, C**H$_2$**-C2), 2.31 – 2.06 (m, 1H, C**H$_2$**-C2), 1.83 (s, 1H, N**H**), 1.47 – 1.43 (m, 9H, OC(C**H$_3$**)$_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 154.2 (**C**OOC(CH_3)$_3$), 149.1, 149.0, 148.2, 148.2, 147.7, 147.3, 146.3, 144.7 (4x**C**-OCH_3), 132.0, 130.9 (**C1'**), 128.4, 125.2, 124.9 (**C6a, C10a**), 121.3, 121.1, 120.9 (**C6'**), 112.8, 112.4, 112.3, 112.2, 111.4, 111.4, 111.3, 111.3, 111.2, 111.1, 111.0, 109.4, 108.9 (**C**H$_{Ar}$), 80.2, 80.1, 80.0, 79.9 (O**C**(CH_3)$_3$), 60.3, 60.0, 59.6 (**C2**), 56.2, 56.1, 56.0, 55.9, 54.5, 54.4 (4xO**C**H_3), 53.2, 52.9 (**C4**), 47.2, 47.1 (**C5**), 39.5, 39.3 (**C**H_2-C2), 32.0, 31.6, 31.4 (**C6**), 28.6 (OC(**C**H_3)$_3$).

5.3.22. General procedure to obtain 4-cyano-5-imino[3]benzazocin 34a–34b.



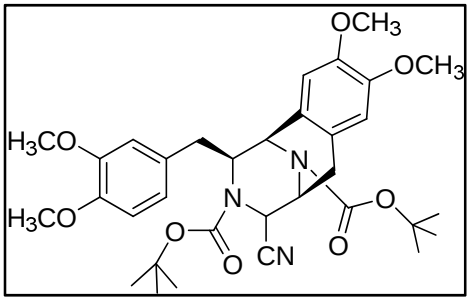
To a solution of **26b** or **27a** (1.0 eq) in dry DCM (39.0 eq) $(Boc)_2O$ (1.2 eq) and DMAP (0.5 eq) were added, and the reaction was stirred at room temperature for 12h. The crude was extracted with DCM (2x 25 mL) and the organic layer was dried over anhydrous Na_2SO_4 filtered, concentrated under reduced pressure and purified by flash column chromatography using diethyl ether to obtain **34a'** and AcOEt to obtain **34b'** as brown oils. These compounds were not characterized due to the complex mixture of rotamers and were used directly in the next reaction.($^tBuO)_3LiAlH$ (5–7 eq) was added to compounds **34a'** and **34b'** (1.0 eq) in dry THF (54 eq), at room temperature and stirred for 72 h. The mixture was poured into a saturated solution of $NaHCO_3$, filtered through celite and washed with DCM (3x25 mL). The mother liquor was extracted with DCM (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. To this crude, KCN (50.0–95.0 eq) and H_2O (200 eq) were added and the reaction was stirred during 10 min. Then, AcOH (160 eq) was added at room temperature and stirred for 12 h. The reaction was quenched with a saturated solution of $NaHCO_3$, extracted with DCM (2 x 10 mL) and purified by flash column chromatography using diethyl ether to obtain **34**.

5.3.22.1. Synthesis of *tert*-butyl 4-cyano-2-(3,4-dimethoxybenzyl)-8,9-dimethoxy-11-methyl-1,2,5,6-tetrahydro-1,5-epiminobenzo[*d*]azocine-3(4*H*)-carboxylate 34a.



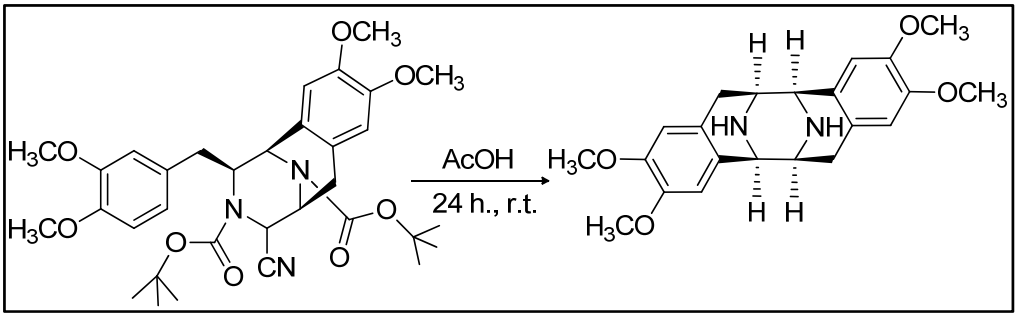
Obtained according to the general procedure **5.3.22** using compound **27a** (0.31 g, 0.75 mmol) as starting material, $(Boc)_2O$ (0.20 g, 0.90 mmol), DMAP (0.046 g, 0.37 mmol), and DCM (1.0 mL) as solvent. Purification by flash column chromatography on silica gel using ethyl acetate as eluent afforded product **34a'** (0.130 g, 0.25 mmol) as a brown oil in 34% yield. (^{t}BuO)$_3$LiAlH (0.47 g, 1.8 mmol) was added to the compound **34a'** (0.13g, 0.25 mmol) in THF (2.0 mL). Then, to this mixture KCN (1.55 g, 0.024 mol) in H_2O (1.0 mL) and AcOH (2.55 mL) was added. Purification by flash column chromatography on silica gel using diethyl ether as eluent afforded product **34a** (0.05 g, 0.01 mmol) as a brown oil in 38% yield; **IR (NaCl)** ν_{max} 3200, 2930, 2100, 1687, 1620 cm^{-1}; **Analysis**: Calcd**.** for $C_{29}H_{37}N_3O_6$: C, 66.52; H, 7.12; N, 8.02. Found: C, 66.40; H, 7.08; N, 8.09.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.82 (s, 0.8H, **H7**), 6.81 (s, 0.2H, **H7**), 6.74 (d, *J* = 5.0 Hz, 2H, C**H$_{Ar}$**), 6.70 – 6.58 (m, 2H, C**H$_{Ar}$**), 4.70 – 4.54 (m, 1H, **H5**), 4.36 – 4.04* (m, 1H, **H1**), 3.85* (dd, *J* = 5.3, 4.5 Hz, 13H, 4xOC**H$_3$**, **H2**), 3.69 (d, *J* = 7.6 Hz, 1H, **H4**), 3.05 (d, *J* = 6.4 Hz, 1H, **H6**), 3.03 – 2.93 (m, 1H, C**H$_2$**-C2), 2.87 (d, *J* = 11.8 Hz, 1H, C**H$_2$**-C2), 2.77 (dd, *J* = 10.2, 6.6 Hz, 1H, **H6**), 2.65 (s, 2H, NC**H$_3$**), 2.51 (s, 1H, NC**H$_3$**), 1.48 – 1.40 (m, 4H, OC(C**H$_3$**)$_3$), 1.27 (d, *J* = 10.7 Hz, 4H, OC(C**H$_3$**)$_3$).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 155.5 (**C**OOC(CH$_3$)$_3$), 149.2, 148.9, 148.3, 147.6 (4x**C**-OCH$_3$), 131.1 (**C1'**), 126.7, 126.5, 126.5 (**C6a, C10a**), 122.0 (**C**N), 121.4, 121.2, 112.9, 112.4, 111.8, 111.5, 111.4, 111.3, 110.9 (**C**H$_{Ar}$), 79.4 (O**C**(CH$_3$)$_3$), 68.8, 68.3 (**C4**), 64.3, 63.6, 62.8, 62.4 (**C5**), 56.3, 56.2, 56.1, 56.0, 55.9 (4xO**C**H$_3$, **C1, C2**), 46.4, 43.8 (N**C**H$_3$), 41.1 (**C6**), 30.3, 29.0 (**C**H$_2$-C2), 28.4, 28.4, 28.3 (OC(**C**H$_3$)$_3$).

5.3.22.2. Synthesis of di-*tert*-butyl (1*R**, 2*S**, 4RS*, 5*S**)-4-cyano-8,9-dimethoxy-2-(3,4-dimethoxybenzyl)-1,2,3,4,5,6-tetrahydro-1,5-imino[3]benzazocin-3,11-dicarboxylate 34b.



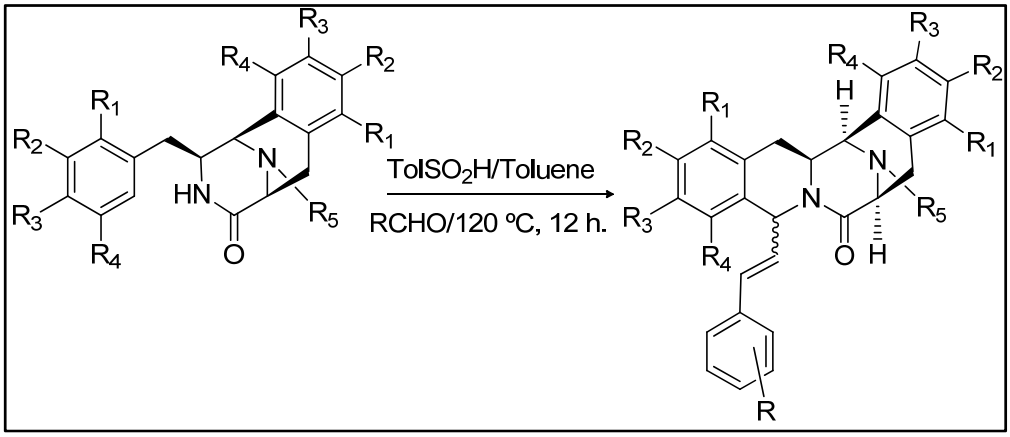
Obtained according to the general procedure **5.3.22** using compound **26b** (0.20 g, 0.40 mmol) as starting material, $(Boc)_2O$ (0.11 g, 0.48 mmol), DMAP (0.024 g, 0.2 mmol), and DCM (1.0 mL) as solvent. Purification by flash column chromatography on silica gel using diethyl ether as eluent afforded product **34b'** (0.134 g, 0.22 mmol) as a brown oil in 55% yield. (^{t}BuO)$_3$LiAlH (0.29 g, 1.12 mmol) was added to compound **34b'** (0.134g, 0.22 mmol) in THF (1.0 mL). Then to this mixture, KCN (0.72 g, 0.011 mol) in H_2O (1.0 mL) and AcOH (2.54 mL) was added. Purification by flash column chromatography on silica gel using diethyl ether as eluent afforded product **34b** (0.134 g, 0.22 mmol) as a brown oil in 99% yield as a mixture of rotamers in $CDCl_3$, 25 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 2010, 1813, 1775cm^{-1}; **Analysis:** Calcd. for $C_{33}H_{43}N_3O_8$: C, 65.01; H, 7.11; N, 6.89. Found: C, 65.00; H, 6.96; N, 6.78; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.93 – 6.70 (m, 3H, C**H$_{Ar}$**), 6.50 (s, 0.6H, **H7**), 6.40 (s, 0.6H, **H7**), 6.30 (s, 0.3H, **H10**), 6.22 (s, 0.7H, **H10**), 5.64 (s, 0.5H, **H5**), 5.57 (s, 0.5H, **H5**), 5.01 (s, 0.5H, **H1**), 4.83 (s, 0.5H, **H1**), 4.65 (m, 1H, **H5**), 4.24 – 4.03 (m, 1H, **H2**), 3.83 – 3.72 (m, 12H, 4xOC**H$_3$**), 3.64 – 3.56 (m, 1H, **H6**), 3.21 – 3.09 (m, 1H, **H6**), 3.06 – 2.94 (m, 1H, C**H$_2$**-C2), 2.90 – 2.70 (m, 1H, C**H$_2$**-C2), 2.88 – 2.74 (m, 1H, C**H$_2$**-C2), 1.49 – 1.18 (m, 18H, 2 x OC(C**H$_3$**)$_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 155.9, 155.5, 154.9, 154.8 (2 x **C**OOC(CH$_3$)$_3$), 149.0, 148.9, 148.8, 148.7, 148.3, 148.1, 147.7, 147.7, 147.5, 147.4, 147.3 (4x**C**-OCH$_3$), 131.8, 131.7 (**C1'**), 128.5, 127.9, 127.7, 127.0, 125.8, 125.5, 125.0 (**C6a, C10a, C**N), 122.0, 121.9, 121.6, 121.4 (**C6'**), 113.2, 112.3, 111.4, 111.3, 111.2, 111.0 (**C**2',C5'), 109.1, 108.6 (**C7**) , 80.8, 80.7, 80.5, 80.3 (2xO**C**(CH$_3$)$_3$), 78.1, 78.0 (**C4**), 60.6, 60.0 (**C2**), 56.3, 56.2, 56.1, 55.9, 55.9, 55.8 (4xO**C**H$_3$), 51.7 (**C1**), 51.3, 49.9 (**C5**), 49.5 (**C1**), 39.7, 39.5 (**C**H$_2$-C2), 30.1, 29.7 (**C6**), 28.4, 28.3, 28.2, 28.1, 28.0 (2xOC(**C**H$_3$)$_3$).

5.3.23. Synthesis of (6*R**,7*S**,13*R**,14*S**)-2,3,9,10-tetramethoxy-5,6,7,12,13,14-hexahydro-6,14:7,13-diepiminodibenzo[*a,f*][10]annulene 35.



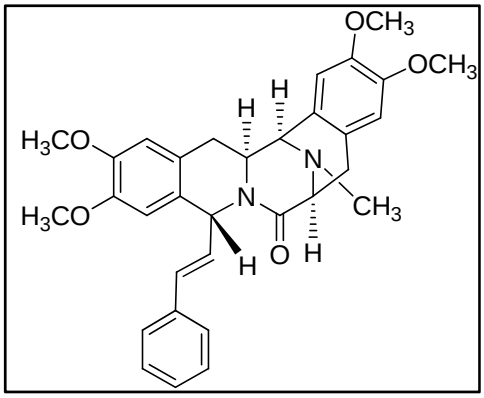
To compound **34b** (0.07 g, 0.12 mmol) AcOH (0.5 mL) at room temperature was added and the reaction was stirred for 24 h. The mixture was quenched with a saturated solution of $NaHCO_3$, extracted with DCM (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purificated by flash column chromatography using a mixture 1:1 ethyl acetate:methanol as eluent to obtain **35** (0.034g, 0.089 mmol) as a brown solid in 75% yield; **Mp** 163–164 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{22}H_{26}N_2O_6$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.00; H, 6.80; N, 7.41; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.74 (s, 2H, **H4, H11**), 6.57 (s, 2H, **H1, H8**), 3.87 (d, *J* = 6.0 Hz, 14H, 4xOC**H**$_3$, **H7**, **H14**), 3.65 (s, 2H, 2xN**H**), 3.37 (dd, *J* = 17.3, 7.6 Hz, 2H, **H12, H5**), 3.12 (d, *J* = 7.6 Hz, 1H, **H13, H6**), 2.94 (d, *J* = 17.3 Hz, 1H, **H12, H5**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 148.3, 147.3 (4x**C**-OCH_3), 130.9, 127.5 (**C4a, C7a, C11a, C14a**), 111.4 (**C11, C4**), 109.3 (**C8, C1**), 58.1 (**C7, C14**), 56.2, 56.1 (4xO**C**H_3), 52.0 (**C6, C13**), 32.6 (**C12, C5**).

5.3.24. General procedure to obtain (6*S**, 9R* o S*, 14a*S**, 15*R**, *E*)-2,3,11,12-tetramethoxy-16-methyl-9-styryl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 36a- 36r.



To a solution of **24a, 27b, 28** or **29** (1.0 eq) in dry toluene, *p*-toluenesulfinic acid (3.0 eq) and aryl aldehyde (2.0 eq) were added (160 eq) at 120 ºC and the mixture was stirred for 12 h. The reaction was quenched with a saturated solution of $NaHCO_3$, extracted with DCM (2x 20 mL), and the organic layer was dried over anhydrous Na_2SO_4 and filtered. The solution was concentrated *in vacuo* and purified by flash column chromatography using a mixture of ethyl acetate:methanol as eluent to obtain compounds **36a – 36s**.

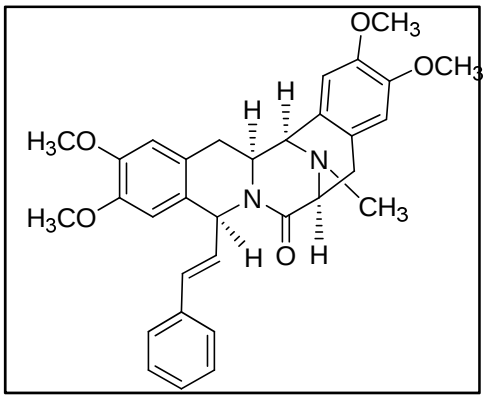
5.3.24.1. Synthesis of (6*S**,9*R**,14a*S**,15*R**)-2,3,11,12-tetramethoxy-16-methyl-9-((*E*)-styryl)-9,14,14a,15-tetrahydro-5*H*-6,15-epiminobenzo[4,5]azocino[1,2-*b*]isoquinolin-7(6*H*)-one 36a.



Obtained according to the general procedure **5.3.24** using compound **27a** (0.15 g, 0.36 mmol) as starting material, cinnamadehyde (0.096 g, 0.72 mmol), *p*-toluenesulfinic acid (0.168 g, 1.08 mmol) and toluene (3.0 mL) as solvent. Purification by flash column chromatography on silica gel using 9:1 ethyl acetate: methanol as eluent afforded product **36a** (0.090 g, 0.017 mmol) as a pale yellow solid in 47% yield; **Mp** 119–120 ºC; **IR (NaCl) ν_{max}** 2930, 1693, 1625

cm^{-1}; **Analysis**: Calcd. for $C_{32}H_{34}N_2O_5$: C, 72.98; H, 6.51; N, 5.32. Found: C, 72.86; H, 6.44; N, 5.31.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.13 – 7.09 (m, 3H, **H3'', H5'', H4''**), 6.85 – 6.81 (m, 2H, **H2'', H6''**), 6.75 (s, 1H, **H1**), 6.71 (s, 1H, **H4**), 6.70 (s, 1H, **H13**), 6.64 (s, 1H, **H10**), 5.83 (d, *J* = 1.3 Hz, 1H, **H9**), 5.80 – 5.75 (m, 1H, **H1'**), 5.42 (d, *J* = 14.8 Hz, 1H, **H2'**), 4.11 (ddd, *J* = 7.1, 4.3, 3.6 Hz, 1H, **H14a**), 3.89 (s, 3H, OC**H$_3$**), 388 (s, 6H, OC**H$_3$**), 3.87 (s, 3H, OC**H$_3$**), 3.85 (d, *J* = 2.0 Hz, 1H, **H15**), 3.76 (d, *J* = 6.0 Hz, 1H, **H6**), 3.32 (dd, *J* = 17.2, 6.3 Hz, 1H, **H5**), 2.90 (d, *J* = 17.2 Hz, 1H, **H5**), 2.72 – 2.64 (m, 2H, **H14**), 2.53 (s, 3H, NC**H$_3$**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 170.2 (**C**O), 148.2, 148.0, 147.8, 147.4 (4x**C**-OCH$_3$), 136.8 (**C1''**), 129.9 (**C1'**), 128.3 (**C3'', C5''**), 128.2* (**C4a**), 127.2 (**C4''**), 126.9* (**C15a**), 126.7 (**C2'**), 126.4 (**C2'', C6''**), 126.3, 122.9 (**C9a, C13a**), 112.5 (**C10**), 111.5 (**C4**), 111.1 (**C13**), 110.4 (**C1**), 61.1 (**C15**), 60.3 (**C6**), 58.6, 56.4, 56.2, 56.2, 55.9, 55.9 (4xO**C**H$_3$, **C9, C14a**), 40.2 (N**C**H$_3$), 32.4 (**C14**), 28.7 (**C5**).

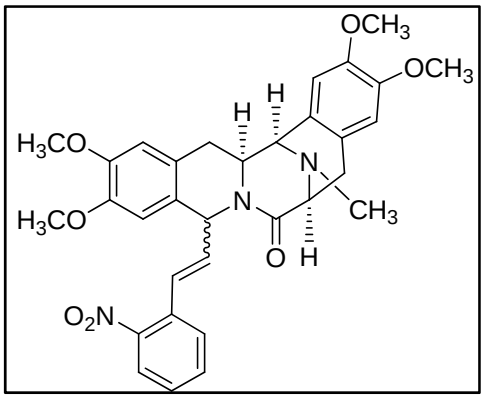
5.3.24.2. Synthesis of (6*S**,9*S**,14a*S**,15*R**,1'*E*)-2,3,11,12-tetramethoxy-16-methyl-9-styryl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 36b.



Obtained according to the general procedure **5.3.24** using compound **27a** (0.05 g, 0.12 mmol) as starting material, cinnamadehyde (0.032 g, 0.24 mmol), *p*-toluenesulfinic acid (0.056 g, 0.36 mmol) and toluene (1.0 mL) as solvent. Purification by flash column chromatography on silica gel using 98:2 ethyl acetate: methanol as eluent afforded product **36b** (0.026 g, 0.049 mmol) as a pale yellow solid in 41% yield; **Mp** 125–126 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{32}H_{34}N_2O_5$: C, 72.98; H, 6.51; N, 5.32. Found: C, 72.90; H, 6.46; N, 5.30; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 4H, C**H$_{Ar}$''**), 7.25 – 7.19 (m, 1H, **H4''**), 6.61 (s, 1H, **H4**), 6.59 (s, 1H, **H10**), 6.57 (s, 1H, **H1**), 6.52 (s, 1H, **H13**), 6.49 (d, *J* = 14.4 Hz, 1H, **H2''**), 6.35 (dd, *J* = 15.7, 6.5 Hz, 1H, **H1''**), 6.15 (d, *J* = 6.5 Hz, 1H, **H9**), 4.33 (ddd, *J* = 11.7, 5.2, 3.8 Hz, 1H, **H14a**), 3.93 (s, 3H, OC**H$_3$**), 3.92 – 3.89 (m, 1H, **H15**), 3.85 (s, 3H, OC**H$_3$**), 3.84 (s, 3H, OC**H$_3$**), 3.77 (s, 3H, OC**H$_3$**), 3.73 (d, *J* = 7.5 Hz, 1H,), 3.18 (dd, *J* = 17.7, 7.4 Hz, 1H, **H6**), 2.87 (d, *J* = 17.5 Hz, 1H, **H6**), 2.67 (dd, *J* = 15.8, 3.7 Hz, 1H, **H14**), 2.50 – 2.43 (m, 4H, N**CH$_3$, H14**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 171.0 (**C**O), 149.1, 148.1, 147.8, 146.9 (4x**C**-OCH$_3$), 136.7 (**C1''**), 133.3 (**C2''**), 128.6 (**C3'', C5''**), 128.4 (**C1'**), 127.9 (**C4''**), 126.9 (**C2'', C6''**), 125.5, 124.7, 124.6, 123.0 (**C4a, C9a, C13a, C15a**), 113.4 (**C10**), 111.5

(**C4**), 110.8, 110.7 (**C13, C1**), 59.9 (**C15**), 59.7 (**C6**), 56.5, 56.1, 56.0, 55.9 (4xOCH_3), 53.8 (**C9**), 51.9 (**C14a**), 40.1 (NCH_3), 33.1 (**C14**), 27.0 (**C5**).

5.3.24.3. Synthesis of (6*S**,9*R**,14a*S**,15*R**,1'*E*) and (6*S**,9*S**,14a*S**,15*R**,*E**)-2,3,11,12-tetramethoxy-16-methyl-9-(2-nitrostyryl)-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 36c and 36d.



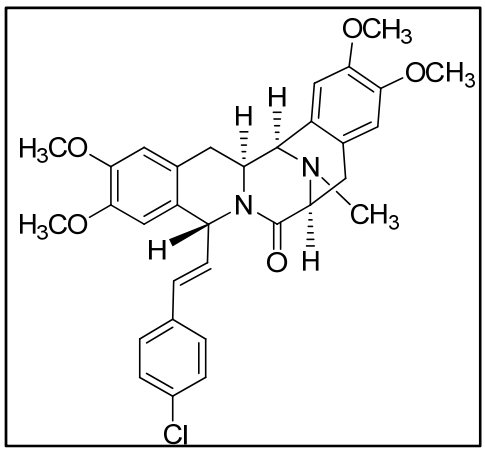
Obtained according to the general procedure **5.3.24** using compound **27a** (0.05 g, 0.12 mmol) as starting material, 2-nitrocinnamadehyde (0.028 g, 0.24 mmol), *p*-toluenesulfinic acid (0.056 g, 0.36 mmol) and toluene (1.0 mL) as solvent. Purification by flash column chromatography on silica gel afforded product **36c** and **36d** as a 1:1 mixture of the 2 diasteromers (0.055 g, 0.096 mmol) as a pale yellow solid in 80% yield; **IR(NaCl) ν_{max}** 3130, 2920, 1693, 1615 cm^{-1}.

***Cis* diasteromer (6*S**,9*R**,14a*S**,15*R**)**: **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.1 Hz, 1H, **H3''**), 7.57 – 7.48 (m, 2H, **H6''**), 7.32 (dd, *J* = 7.5, 1.4 Hz, 1H, **H5''**), , 6.91 (dd, *J* = 7.9, 1.4 Hz, 1H, **H4''**), 6.86 (dd, *J* = 15.5, 0.6 Hz, 1H, **H2'**), 6.68 (s, 1H, C**H**$_{Ar}$), 6.60 (s, 2H, C**H**$_{Ar}$), 6.50 (s, 1H, C**H**$_{Ar}$), 6.25 (dd, *J* = 15.4, 6.5 Hz, 1H, **H1'**), 6.14 (d, *J* = 6.5 Hz, 1H, **H9**), 4.35 (ddd, *J* = 11.7, 5.0, 3.8 Hz, 1H, **H14a**), 3.95 (d, *J* = 5.1 Hz, 1H, **H15**), 3.91 – 3.77 (s, 12H, 4xOC**H$_3$**), 3.75 – 3.71 (m, 1H, **H6**), 3.11 (dd, *J* = 13.6, 7.3 Hz, 1H, **H5**), 2.86 (d, *J* = 14.1 Hz, 1H, **H5**), 2.68 (dd, *J* = 11.4, 3.3 Hz, 1H, **H14**), 2.46 (s, 3H, NC**H$_3$**), 2.46 – 2.48 (m, 1H, **H14**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 171.0 (**C**O), 149.0, 148.2, 147.9, 147.2 (4x**C**-OCH_3), 133.3, 133.2 (**C1', C6''**), 133.2 (**C1''**), 129.4 (**C2', C4'**), 128.3 (**C5''**), 128.5, 125.3, 124.6* (**C4a, C9a, C13a**), 124.6 (**C3''**), 123.7, 122.7* (**C15a, C2''**), 113.4, 111.4, 110.7, 110.5 (**C**H$_{Ar}$), 59.8, 59.7 (**C15, C6**), 58.6, 56.4, 55.9 (4xO**C**H_3), 53.6 (**C9**), 52.2 (**C14a**), 40.0 (N**C**H_3), 33.0 **(C14)**, 29.3 **(C5)**.

***Trans* diasteromer (6*S**,9*S**,14a*S**,15*R**)**: **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.80* (dd, *J* = 8.1, 1.3 Hz, 1H, **H4'', H5''**), 7.57 – 7.48** (m, 2H, **H6'', H3''**), 7.39 – 7.35** (m, 1H, **H6'', H3''**), 7.21* (dd, *J* = 7.4, 1.2 Hz, 1H, **H4'', H5''**), 6.75 (s, 1H, C**H**$_{Ar}$), 6.74 (s, 1H, C**H**$_{Ar}$), 6.60 (s, 1H, C**H**$_{Ar}$), 6.56 (s, 1H, C**H**$_{Ar}$), 5.93 (d, *J* = 15.9 Hz, 1H, **H2''**), 5.89 (d, *J* = 4.5 Hz, 1H, **H9**), 5.68 (dd, *J* = 15.6, 4.3 Hz, 1H, **H1'**), 4.09 (dt, *J* = 7.2, 3.8 Hz, 1H, **H14a**), 3.91 – 3.77 (s, 13H, 4xOC**H$_3$, H15**), 3.75 – 3.71 (m, 1H, **H6**), 3.26 (dd, *J* = 16.5, 5.5 Hz, 1H, **H5**), 2.97 (d, *J* = 16.5 Hz, 1H, **H5**), 2.74 (dd, *J* = 9.4, 3.8 Hz, 1H, **H14**), 2.48 (s, 3H, NC**H$_3$**), 2.46 – 2.48 (m, 1H, **H14**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 170.5 (**C**O), 148.8, 148.3, 147.7, 146.9 (4x**C**-OCH_3), 134.8 (**C1'**), 133.5 (**C1''**), 133.0, 129.4 (**C3'',**

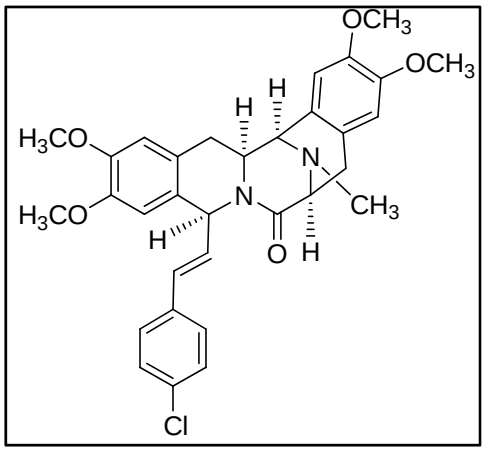
C6'') , 127.8* (**C5''**), 126.0, 125.9, 125.5** (**C4a, C9a, C13a**), 124.5* (**C4''**), 124.1 (**C2'**), 122.4, 121.8** (**C15a, C2''**), 112.2, 111.4, 111.0, 110.6 (CH_{Ar}), 60.9 (**C15**), 60.2 (**C6**), 56.2, 56.1, 56.1, 56.0 (4xOCH_3), 55.9, 55.7 (**C14a, C9**), 40.1 (NCH_3), 32.3 (**C14**), 29.8 **(C5).**

5.3.24.4. Synthesis of (6*S**,9*R**,14a*S**,15*R**,1'*E*)-9-(4-chlorostyryl)-2,3,11,12-tetramethoxy-16-methyl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 36e.



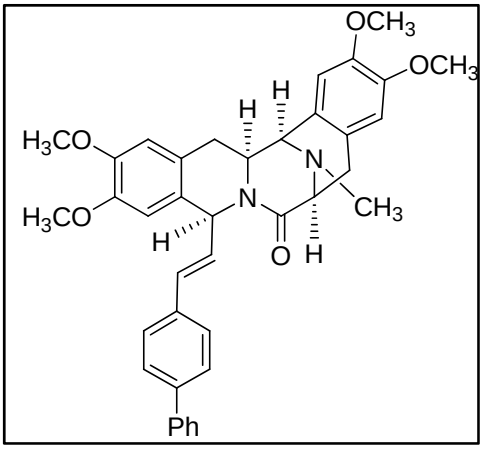
Obtained according to the general procedure **5.3.24** using compound **27a** (0.05 g, 0.12 mmol) as starting material, 4-chlorocinnamadehyde (0.040 g, 0.24 mmol), *p*-toluenesulfinic acid (0.056 g, 0.36 mmol) and toluene (1.0 mL) as solvent. Purification by flash column chromatography on silica gel using 9:1 ethyl acetate:methanol as eluent afforded product **36e** (0.037 g, 0.07 mmol) as a brown solid in 58% yield; **Mp** 128 – 129 ºC; **IR (NaCl)** ν_{max} 2930, 2320, 1673, 1610 cm^{-1}; **Analysis**: Calcd. for $C_{32}H_{33}N_2$: C, 68.50; H, 5.93; N, 4.99. Found: C, 68.32; H, 5.80; N, 5.09.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.08* (d, *J* = 8.5 Hz, 2H, **H3'', H5''**), 6.74* (d, *J* = 8.5 Hz, 3H, **H2'', H6'',** CH_{Ar}), 6.63 – 6.59 (m, 2H, CH_{Ar}), 5.83 (d, *J* = 4.9 Hz, 1H, **H9**), 5.76 (dd, *J* = 15.3, 4.5 Hz, 1H, **H1'**), 5.34 (d, *J* = 15.4 Hz, 1H, **H2'**), 4.13 – 4.02 (m, 1H, **H14a**), 3.91 – 3.82 (m, 13H, 4xOCH_3, **H15**), 3.75 (d, *J* = 6.3 Hz, 1H, **H6**), 3.31 (dd, *J* = 17.5, 6.4 Hz, 1H, **H5**), 3.25 – 3.13 (m, 1H, **H14**), 2.88 (d, *J* = 17.2 Hz, 1H, **H5**), 2.72 (dd, *J* = 10.8, 3.5 Hz, 1H, **H14**), 2.52 (s, 3H, NCH_3).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 170.2 (CO), 149.2, 148.3, 148.3, 147.4 (4xC-OCH_3), 135.4 (**C1''**), 132.8 (**C4''**), 130.6 (**C1'**), 128.4* (**C2'', C6''**), 128.1** (**C4a, C9a**), 127.6* (**C3'', C5''**), 126.6, 126.3 (***C4a, *C9a, *C13a, *C15a**), 125.6 (**C2'**), 122.9** (**C13a, C15a**), 112.6, 111.5, 111.1, 110.4 (CH_{Ar}), 61.0 (**C15**), 60.2 (**C6**), 58.7 (**C9**), 56.4, 56.2, 56.2, 55.9, 55.8 (4xOCH_3, **C14a**), 40.1 (NCH_3), 32.4 (**C14**), 28.6 (**C5**).

5.3.24.5. Synthesis of (6*S**,9*S**,14a*S**,15*R**,1'*E*)-9-(4-chlorostyryl)-2,3,11,12-tetramethoxy-16-methyl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 36f.



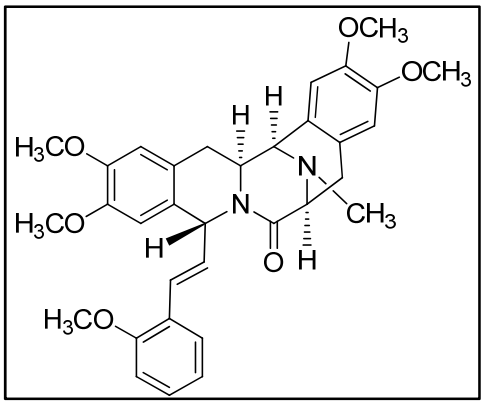
Obtained according to the general procedure **5.3.24** using compound **27a** (0.05 g, 0.12 mmol) as starting material, 4-chlorocinnamadehyde (0.040 g, 0.24 mmol), *p*-toluenesulfinic acid (0.056 g, 0.36 mmol) and toluene (1 mL) as solvent. Purification by flash column chromatography on silica gel using 98:2 ethyl acetate:methanol as eluent afforded product **36f** (0.018 g, 0.03 mmol) as a brown solid in 25% yield; **Mp** 108 – 110 ºC; **IR (NaCl) ν_{max}** 2930, 2320, 1673, 1610 cm^{-1}; **Analysis:** Calcd. for $C_{32}H_{33}N_2O_5$: C, 68.50; H, 5.93; N, 4.99. Found: C, 68.45; H, 5.74; N, 5.02; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.32* (d, *J* = 6.0 Hz, 2H, **H2'', H6''**), 6.68 (s, 1H, C**H**$_{Ar}$), 6.66 (s, 1H, C**H**$_{Ar}$), 6.60* (d, *J* = 6.4 Hz, 2H, **H3'', *H5''**), 6.55 (s, 1H, C**H**$_{Ar}$), 6.52 (s, 1H, C**H**$_{Ar}$), 6.45 (d, *J* = 16.0 Hz, 1H, **H2'**), 6.31 (dd, *J* = 15.6, 6.6 Hz, 1H, **H1'**), 6.12 (d, *J* = 6.8 Hz, 1H, **H9**), 4.21 (dd, *J* = 5.9, 2.7 Hz, 1H, **H14a**), 3.96 – 3.94 (m, 4H, OC**H$_3$, H15**), 3.85 (s, 3H, OC**H$_3$**), 3.85 (s, 3H, OC**H$_3$**), 3.77 (s, 3H, OC**H$_3$**), 3.74 (d, *J* = 8.2 Hz, 1H, **H5**), 3.18 (dd, *J* = 18.0, 7.3 Hz, 1H, **H6**), 2.87 (d, *J* = 17.6 Hz, 1H, **H6**), 2.66 (d, *J* = 15.3 Hz, 1H, **H14**), 2.45 (s, 3H, NC**H$_3$**), 2.32 – 2.27 (m, 1H, **H14**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 170.8 (**C**O), 148.9, 148.1, 147.8, 147.1 (4x**C**-OCH$_3$), 132.7 (**C1''**), 128.9, 128.5 (**C1', C2'**), 128.4, 127.6 (**C2'', C3'', C5'', C6''**), 125.9, 125.7, 123.5, 122.9, 122.3 (**C4'', C4a, C9a, C13a, C15a**), 112.9, 111.6, 110.8, 109.5 (**C**H$_{Ar}$), 60.2, 59.6 (**C15, C6**), 56.4, 56.4, 56.1, 56.1 (4xOC**H$_3$**), 56.0 (**C9**), 53.9 (**C14a**), 40.0 (N**C**H$_3$), 33.5 (**C14**), 29.4 (**C15**).

5.3.24.6. Synthesis of (6*S,9*S**,14a*S**,15*R**,1'*E*)-9-(2-(1,1'-biphenyl-4-yl)vinyl)-2,3,11,12-tetramethoxy-16-methyl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 36g.**



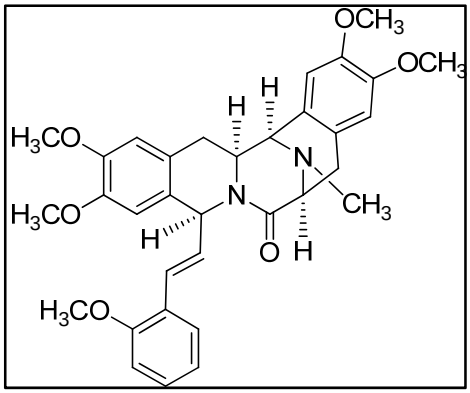
Obtained according to the general procedure **5.3.24** using compound **27a** (0.05 g, 0.12 mmol) as starting material, 4-phenylcinnamadehyde (0.050 g, 0.24 mmol), *p*-toluenesulfinic acid (0.056 g, 0.36 mmol) and toluene (1.0 mL) as solvent. Purification by flash column chromatography on silica gel using 98:2 ethyl acetate:methanol as eluent afforded product **36g** (0.051 g, 0.085 mmol) as a brown solid in 71% yield.; **Mp** 123–124 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 2310 cm^{-1}; **Analysis**: Calcd. for $C_{38}H_{38}N_2O_5$: C, 75.72; H, 6.35; N, 4.65. Found: C, 75.65; H, 6.40; N, 4.59; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.62 – 7.50 (m, 4H, C**H$_{Ar}$**), 7.50 – 7.40 (m, 4H. C**H$_{Ar}$**), 7.35 (d, *J* = 7.1 Hz, 1H, C**H$_{Ar}$**), 6.62 (s, 1H, **H7**), 6.59 (s, 2H, **H10, H1**), 6.54 (d, *J* = 16.0 Hz, 1H, **H2''**), 6.53 (s, 1H, **H13**), 6.41 (dd, *J* = 15.6, 6.4 Hz, 1H, **H1'**), 6.18 (d, *J* = 6.3 Hz, 1H, **H9**), 4.49 – 4.24 (m, 1H, **H14a**), 3.95 – 3.78 (m, 1H, **H15**), 3.95 (s, 3H, OC**H$_3$**), 3.86 (s, 3H, OC**H$_3$**), 3.85 (s, 3H, OC**H$_3$**), 3.78 (s, 3H, OC**H$_3$**), 3.74 (d, *J* = 7.5 Hz, 1H, **H6**), 3.19 (dd, *J* = 17.6, 7.2 Hz, 1H, **H5**), 2.89 (d, *J* = 17.8 Hz, 1H, **H5**), 2.68 (dd, *J* = 15.8, 3.0 Hz, 1H, **H14**), 2.59 – 2.32 (m, 1H, **H14**), 2.47 (s, 3H, NC**H$_3$**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 171.0 (**C**O), 149.1, 148.2, 147.8, 146.9 (4x**C**-OCH$_3$), 140.7, 140.6 (**C4'', C1'''**), 135.8 (**C1''**), 132.8 (**C2'**), 128.9* (**C2'', C3''**), 128.6 (**C1'**), 127.5 (**C4'''**), 127.3, 127.2, 127.0* (**C5'', C6'', C2''', C3''', C5''', C6'''**), 125.5, 124.7, 124.7, 123.0 (**C4a, C9a, C13a, C15a**), 113.4 (**C10**), 111.5 (**C4**), 110.7, 110.7 (**C10, C13**), 59.9, 59.7 (**C15, C6**), 56.5, 56.1, 56.0, 53.8 (**C9**), 51.9 (**C14a**), 40.2 (N**C**H$_3$), 33.2 (**C14**), 27.0 (**C6**).

5.3.24.7. Synthesis of (6*S**,9*S**,14a*S**,15*R**,1'*E*)-9-(2-(1,1'-biphenyl-4-yl)vinyl)-2,3,11,12-tetramethoxy-16-methyl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 36i.



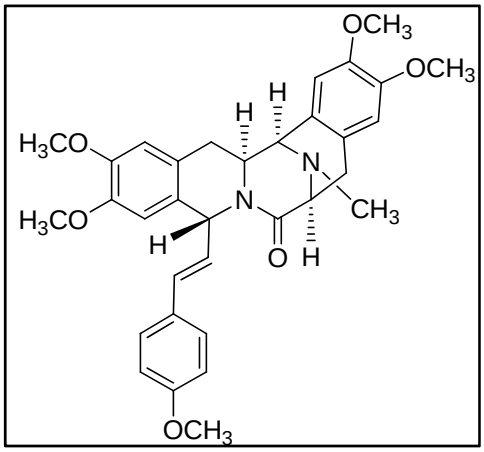
Obtained according to the general procedure 5.3.24 using compound 27a (0.05 g, 0.12 mmol) as starting material, 2-methoxycinnamadehyde (0.039 g, 0.24 mmol), *p*-toluenesulfinic acid (0.056 g, 0.36 mmol) and toluene (2.0 mL) as solvent. Purification by flash column chromatography on silica gel using 9:1 ethyl acetate: methanol as eluent afforded product 36h (0.024 g, 0.043 mmol) as a brown solid in 36% yield; **Mp** 130–131 ºC; **IR (NaCl) ν_{max}** 2930, 2305, 1693, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{33}H_{36}N_2O_6$: C, 71.20; H, 6.52; N, 5.03. Found: C, 71.05; H, 6.60; N, 5.19.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.19 – 7.03 (m, 1H, C**H**$_{Ar}$), 6.85 (d, *J* = 8.2 Hz, 1H, C**H**$_{Ar}$), 6.70 (s, 1H, C**H**$_{Ar}$), 6.61 (m, 5H, C**H**$_{Ar}$), 6.58 (s, 1H, C**H**$_{Ar}$), 6.54 (dd, *J* = 8.0, 1.7 Hz, 1H, **H1'**), 4.83 (d, *J* = 8.4 Hz, **H9**), 4.70 (dd, *J* = 10.2, 6.1 Hz, 1H, **H14a**), 3.93 – 3.92 (m, 1H, **H15**), 3.92 (s, 3H, OC**H**$_3$), 3.88 (s, 3H, OC**H**$_3$), 3.87 (s, 3H, OC**H**$_3$), 3.82 (s, 3H, OC**H**$_3$), 3.67 (d, *J* = 7.0 Hz, **H6**), 3.61 (s, 3H, OC**H**$_3$), 3.11 (dd, *J* = 15.3, 6.3 Hz, 1H, **H5**), 2.88 (d, *J* = 16.0 Hz, 1H, **H5**), 2.76 (dd, *J* = 14.4, 6.0 Hz, 1H, **H14**), 2.49 (s, 3H, NC**H**$_3$), 2.39 (d, *J* = 14.0 Hz, 1H, **H14**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 170.9 (**C**O), 157.0 (**C2''**), 152.4, 148.9, 147.0, 144.7 (4x**C**-OCH_3), 135.1, 133.3, 131.7, 128.2* (**C4a, C9a, C12a, C15a**), 127.6** (**C2'**), 127.1 (**C1'**), 126.0* (**C1''**), 122.5, 120.0, 112.9, 112.8, 111.6, 110.3, 109.9, 109.5** (**C**H_{Ar}), 60.3 , 60.2 (**C15, C**H_3O- C2''), 59.6 (**C6**), 57.8, 56.4, 56.1, 56.0 (4x O**C**H_3), 55.4 (**C14a**), 41.0 (**C9**), 39.9 (N**C**H_3), 33.7 (**C14**), 28.6 (**C5**).

5.3.24.8. Synthesis of (6*S*,9*S*,14a*S*,15*R,1'*E*)-2,3,11,12-tetramethoxy-9-(2-methoxystyryl)-16-methyl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 36j.**



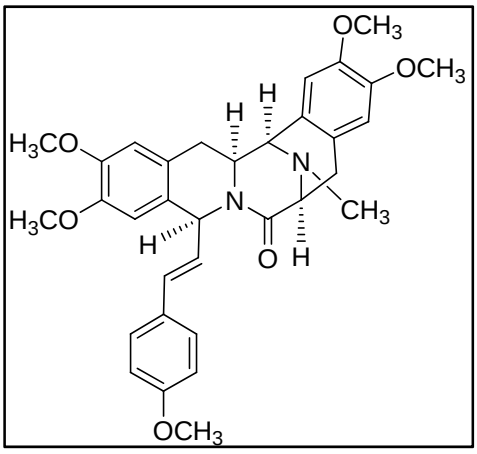
Obtained according to the general procedure 5.3.24 using compound 27a (0.05 g, 0.12 mmol) as starting material, 2-methoxycinnamadehyde (0.039 g, 0.24 mmol), *p*-toluenesulfinic acid (0.056 g, 0.36 mmol) and toluene (0.8 mL) as solvent. Purification by flash column chromatography on silica gel using 98:2 ethyl acetate: methanol as eluent afforded product 36j (0.017 g, 0.030 mmol) as a brown solid in 25% yield; **Mp** 100–101 ºC; **IR (NaCl) ν_{max}** 2950, 2190, 1693, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{33}H_{36}N_2O_6$: C, 71.20; H, 6.52; N, 5.03 Found: C, 71.10; H, 6.50; N, 5.09; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 7.6, 1.6 Hz, 1H, **H6''**), 7.23 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 1H, **H5''**), 6.94 – 6.84 (m, 3H, **H4'', H3'', H2'**), 6.64 (s, 2H, **H4, H10**), 6.62 (s, 1H, **H1**), 6.54 (s, 1H, **H13**), 6.39 (dd, *J* = 15.8, 7.1 Hz, 1H, **H1'**), 6.18 (d, *J* = 7.0 Hz, 1H, **H9**), 4.45 – 4.31 (m, 1H, **H14a**), 3.98 – 3.94 (m, 1H, **H15**), 3.96 (s, 3H, OC**H$_3$**), 3.88 (s, 3H, OC**H$_3$**), 3.87 (s, 3H, OC**H$_3$**), 3.83 (s, 3H, OC**H$_3$**), 3.80 (s, 3H, OC**H$_3$**), 3.76 (d, *J* = 7.5 Hz, 1H, **H6**), 3.21 (dd, *J* = 17.6, 7.4 Hz, 1H, **H5**), 2.92 (d, *J* = 17.5 Hz, 1H, **H5**), 2.70 (dd, *J* = 15.7, 3.6 Hz, 1H, **H14**), 2.51 (s, 3H, NC**H$_3$**), 2.50 – 2.38 (m, 1H, **H14**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 171.2 (**C**O), 157.3 (**C1''**), 149.4, 148.3, 148.0, 147.2 (4x**C**-OCH_3), 129.2, 129.1 (**C1', C5''**), 128.4 (**C2'**), 127.4 (**C6''**), 126.1, 125.8, 125.3, 124.8, 123.5 (**C4a, C9a, C13a, C15a, C1''**), 120.9* (**C3''**), 113.6, 111.8** (**C1, C4**), 111.3* (**C4''**), 111.2 (**C13**), 111.0** (**C10**), 60.1, 60.0 (**C6, C15**), 56.8, 56.4, 56.3, 56.3, 55.9 (5xO**C**H_3), 54.6 (**C9**), 52.0 (**C14a**), 40.5 (N**C**H_3), 33.5 (**C14**), 27.6 (**C5**).

5.3.24.9. Synthesis of (6*S,9*R**,14a*S**,15*R**,1'*E*)-2,3,11,12-tetramethoxy-9-(4-methoxystyryl)-16-methyl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 36k.**



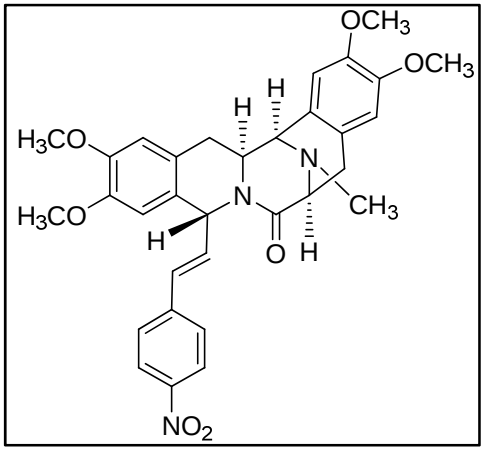
Obtained according to the general procedure 5.3.24 using compound 27a (0.05 g, 0.12 mmol) as starting material, 4- methoxycinnamadehyde (0.039 g, 0.24 mmol), *p*-toluenesulfinic acid (0.056 g, 0.36 mmol) and toluene (0.5 mL) as solvent. Purification by flash column chromatography on silica gel using 90:10 ethyl acetate: methanol as eluent afforded product 36k (0.016 g, 0.029 mmol) as a brown solid in 24% yield; **Mp** 114–115 ºC; **IR(NaCl) ν_{max}** 2930, 2290 cm^{-1}; **Analysis**: Calcd. for $C_{33}H_{36}N_2O_6$: C, 71.20; H, 6.52; N, 5.03. Found: C, 71.11; H, 6.43; N, 4.98.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.79 (d, *J* = 7.7 Hz, 2H, C**H$_{Ar}$**), 6.74 (s, 1H, **H10**), 6.70 (s, 1H, **H4**), 6.67 (s, 1H, C**H$_{Ar}$**), 6.66 (s, 1H, C**H$_{Ar}$**), 6.64 (s, 1H, C**H$_{Ar}$**), 6.54 (s, 1H, C**H$_{Ar}$**), 5.81 (d, *J* = 4.3 Hz, 1H, **H9**), 5.63 (dd, *J* = 15.8, 4.5 Hz, 1H, **H1'**), 5.36 (d, *J* = 15.7 Hz, 1H, **H2''**), 4.16 – 4.09 (m, 1H, **H14a**), 3.87 (m, 13H, 4x OC**H$_3$**, **H15**), 3.77 (d, *J* = 6.1 Hz, 1H, **H6**), 3.71 (s, 3H, OC**H$_3$**), 3.31 (dd, *J* = 16.8, 6.1 Hz , 1H, **H5**), 2.96 (dd, *J* = 16.5, 2.4 Hz, 1H, **H5**), 2.68 (d, *J* = 11.6 Hz, 1H, **H14**), 2.54 (s, 1.5H, NC**H$_3$**), 2.51 (s, 1.5H, NC**H$_3$**), 2.50 – 2.46 (m, 1H, **H14**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 168.8 (**C**O), 158.9 (**C4''**), 149.6, 149.4, 148.4, 148.2, 147.6, 147.2 (4x**C**-OCH_3, **C1''**), 129.5, 128.3, 127.6* (**C9a, C13a, C15a**), 127.5 (**C**H$_{Ar}$), 127.5 (**C1'**), 127.0* (**C4a**), 126.4 (**C1'**), 112.4, 111.8, 111.1, 110.4 (**C**H$_{Ar}$), 61.0 (**C15**), 58.9 (**C6**), 56.2, 56.1, 56.1, 56.0, 56.0 (5xO**C**H$_3$), 55.9 (**C14a**), 55.3 (**C9**), 39.8 (N**C**H$_3$), 38.6 (**C14**), 29.8 (**C5**).

5.3.24.10. Synthesis of (6*S,9*S**,14a*S**,15*R**,1'*E*)-2,3,11,12-tetramethoxy-9-(4-methoxystyryl)-16-methyl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 36m.**



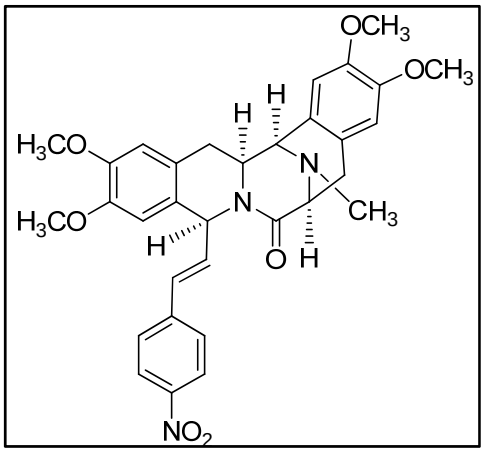
Obtained according to the general procedure **5.3.24** using compound **27a** (0.05 g, 0.12 mmol) as starting material, 4-methoxycinnamadehyde (0.039 g, 0.24 mmol), *p*-toluenesulfinic acid (0.056 g, 0.36 mmol) and toluene (0.5 mL) as solvent. Purification by flash column chromatography on silica gel using 9:1 ethyl acetate: methanol as eluent afforded product **36m** (0.016 g, 0.029 mmol) as a brown solid in 24% yield; **Mp** 118–119 ºC; **IR(NaCl) ν_{max}** 2930, 2330cm^{-1}; **Analysis**: Calcd. for $C_{33}H_{36}N_2O_6$: C, 71.20; H, 6.52; N, 5.03. Found: C, 71.09; H, 6.50; N, 5.01.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.8 Hz, 2H, **H2'', H6''**), 6.83 (d, *J* = 8.8 Hz, 2H, **H3'', H5''**), 6.61 (s, 1H, **H4**), 6.59 (s, 1H, **H1**), 6.57 (s, 1H, **H10**), 6.51 (s, 1H, **H13**), 6.43 (d, *J* = 15.2 Hz, 1H, **H2'**), 6.22 (dd, *J* = 15.3, 6.8 Hz, 1H, **H1'**), 6.13 (d, *J* = 6.9 Hz, 1H, **H9**), 4.38 – 4.27 (m, 1H, **H14a**), 3.94 – 3.91 (m, 4H, **H15,** O**CH$_3$**), 3.85 (s, 1H, O**CH$_3$**), 3.79 (s, 3H, O**CH$_3$**), 3.77 (s, 3H, O**CH$_3$**), 3.18 (dd, *J* = 17.3, 7.5 Hz, 1H, **H5**), 2.88 (d, *J* = 17.5 Hz, 1H, **H5**), 2.66 (dd, *J* = 15.8, 3.4 Hz, 1H, **H14**), 2.46 (s, 3H, N**CH$_3$**), 2.39 – 2.26 (m, 1H, **H14**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 170.9 (**C**O), 159.5 (**C4''**), 149.1, 148.1, 147.8, 146.9 (4x**C**-OCH$_3$), 132.8 (**C1'**), 129.5* (**C1''**), 128.0 (**C2'', C6''**), 126.4 (**C2'**), 125.5, 125.0, 124.6, 123.1* (**C4a, C9a, C13a, C15a**), 114.0 (**C3'', C5''**), 113.4 (**C1**), 111.5 (**C13**), 110.7, 110.7 (**C4, C10**), 59.9, 59.7 (**C6, C15**), 56.5, 56.1, 56.0, 56.0, 55.4 (5xO**C**H$_3$), 53.8 (**C9**), 51.7 (**C14a**), 40.2 (N**C**H$_3$), 33.2 (**C14**), 27.0 (**C5**).

5.3.24.11. Synthesis of (6*S,9*R**,14a*S**,15*R**,1'*E*)-2,3,11,12-tetramethoxy-16-methyl-9-(4-nitrostyryl)-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 36n.**



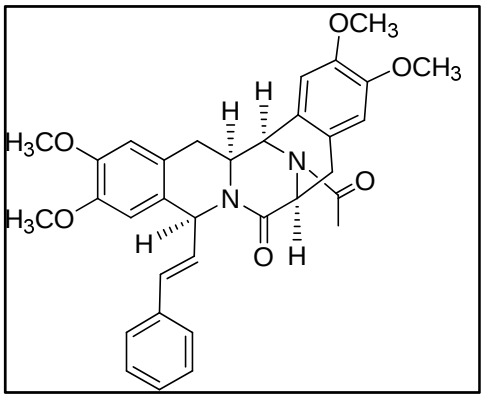
Obtained according to the general procedure **5.3.24** using compound **27a** (0.05 g, 0.12 mmol) as starting material, 4-nitrocinnamadehyde (0.043 g, 0.24 mmol), *p*-toluenesulfinic acid (0.056 g, 0.36 mmol) and toluene (2 mL) as solvent. Purification by flash column chromatography on silica gel using 9:1 ethyl acetate: methanol as eluent afforded product **36n** (0.011 g, 0.019 mmol) as a brown oil in 16% yield; **IR (NaCl) ν_{max}** 2930, 2300, 1693, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{32}H_{33}N_3O_7$: C, 67.24; H, 5.82; N, 7.35. Found: C, 67.09; H, 5.71; N, 7.44; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.9 Hz, 2H, **H3'', H5''**), 6.94 (d, *J* = 8.9 Hz, 2H, **H3'', H5''**), 6.76 (s, 1H, **CH_{Ar}**), 6.73 (s, 1H, **CH_{Ar}**), 6.72 (s, 1H, **CH_{Ar}**), 6.65 (s, 1H, **CH_{Ar}**), 6.64 (s, 1H, **CH_{Ar}**), 6.00 (dd, *J* = 15.9, 4.4 Hz, 1H, **H1'**), 5.87 (dd, *J* = 4.4, 0.9 Hz, 1H, **H9**), 5.41 (dd, *J* = 15.8, 1.1 Hz, 1H, **H2'**), 4.18 – 4.09 (td, *J* = 15.8, 1.1 Hz, 1H, **H14a**), 3.90 (m, 3H, OCH_3), 3.89 (m, 3H, OCH_3), 3.87 (m, 3H, OCH_3), 3.86 (m, 3H, OCH_3), 3.81 – 3.74 (m, 1H, **H6**), 3.33 (dd, *J* = 17.2, 6.4 Hz, 1H, **H5**), 2.90 (dd, *J* = 16.3, 6.8 Hz, 1H, **H6**), 2.70 (dd, *J* = 15.3, 3.0 Hz, 1H, **H14**), 2.58 – 2.42 (m, 4H, NCH_3, **H14**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 170.4 (**C**O), 149.2, 148.5, 148.4, 147.4, 146.6 (4x**C**-OCH_3, **C1''**), 143.5 (**C4''**), 134.9 (**C1'**), 128.5* (**C4a**), 126.9 (**C2'', C6''**), 126.4, 125.8* (**C9a, C13a**), 124.6 (**C2'**), 123.7 (**C3'', C5''**), 122.9* (**C15a**), 112.6, 111.4, 111.2, 110.3 (CH_{Ar}), 60.9, 60.3 (**C6, C15a**), 58.8 (**C14a**), 56.4, 56.2, 56.2, 56.0, 55.8 (4xOCH_3, **C9**), 40.2 (NCH_3), 32.4 (**C14**), 28.6 (**C5**).

5.3.24.12. Synthesis of (6*S,9*S**,14a*S**,15*R**)-2,3,11,12-tetramethoxy-16-methyl-9-((*E*)-4-nitrostyryl)-9,14,14a,15-tetrahydro-5*H*-6,15-epiminobenzo[4,5]azocino[1,2-*b*]isoquinolin-7(6*H*)-one 36o.**



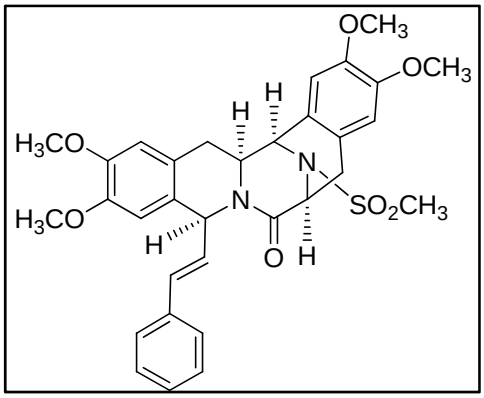
Obtained according to the general procedure 5.3.24 using compound 27a (0.05 g, 0.12 mmol) as starting material, 4-nitrocinnamadehyde (0.043 g, 0.24 mmol), *p*-toluenesulfinic acid (0.056 g, 0.36 mmol) and toluene (2.0 mL) as solvent. Purification by flash column chromatography on silica gel using 9:1 ethyl acetate:methanol as eluent afforded product 36o (0.032 g, 0.056 mmol) as a brown solid in 47% yield.; **Mp** 130–131 ºC; **IR (NaCl) ν_{max}** 2930, 2305, 1693, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{32}H_{33}N_3O_7$: C, 67.24; H, 5.82; N, 7.35. Found: C, 67.21; H, 5.76; N, 7.25; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.8 Hz, 2H, **H3, H5**), 7.49 (d, *J* = 8.8 Hz, 2H, **H2, H6**), 6.62 – 6.54 (m, 5H, **CH_{Ar}, H2'**), 6.51 – 6.42 (m, 1H, **H1'**), 6.14 (d, *J* = 6.3 Hz, 1H, **H9**), 4.31 (ddd, *J* = 11.7, 5.3, 3.8 Hz, 1H, **H14a**), 3.95 – 3.92 (m, 4H, OC**H_3, H15**), 3.86 (s, 3H, OC**H_3**), 3.85 (s, 3H, OC**H_3**), 3.77 (s, 3H, OC**H_3**), 3.75 (d, *J* = 7.5 Hz, 1H, **H6**), 3.19 (dd, *J* = 17.7, 7.4 Hz, 1H, **H5**), 2.86 (d, *J* = 17.7 Hz, 1H, **H5**), 2.69 (dd, *J* = 15.7, 3.6 Hz, 1H, **H14**), 2.53 – 2.40 (m, 4H, **H9,** N**H_3**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 171.1 (**C**O), 149.2, 148.4, 148.0 (3x**C**-OCH_3), 147.1, 147.0 (**C**-OCH_3, **C1''**), 143.2 (**C4''**), 133.2 (**C1'**), 131.0 (**C2'**), 127.4 (**C2'', C6''**), 125.3, 124.7* (**C4a, C9a**), 124.0 (**C3'', C5''**), 123.8, 122.4* (**C13a, C15a**), 113.5, 111.5, 110.9, 110.5 (**C**H_{Ar}), 59.9, 59.7 (**C5, C14**), 56.5, 56.2, 56.0, 55.9 (4xO**C**H_3), 53.7 (**C9**), 52.7 (**C14a**), 40.0 (N**C**H_3), 33.0 (**C14**), 26.4 (**C5**).

5.3.24.13. Synthesis of (6*S,9*R**,14a*S**,15*R**,1'*E*)-2,3,11,12-tetramethoxy-16-methyl-9-(4-nitrostyryl)-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 36p.**



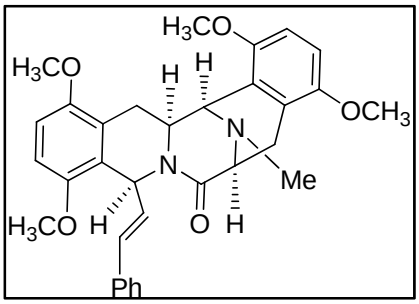
Obtained according to the general procedure **5.3.24** using compound **30** (0.10 g, 0.23 mmol) as starting material, cinnamadehyde (0.061 g, 0.46 mmol), *p*-toluenesulfinic acid (0.107 g, 0.69 mmol) and toluene (1.0 mL) as solvent. Purification by flash column chromatography on silica gel using 98:2 ethyl acetate:methanol as eluent afforded product **36p** (0.034 g, 0.061 mmol) as a brown solid in 27% yield; **Mp** 140–141 ºC; **IR (NaCl) ν_{max}** 2930, 2320 cm^{-1}; **Analysis**: Calcd.for $C_{27}H_{34}N_2O_6$: C, 71.46; H, 6.18; N, 5.05. Found: C, 71.40; H, 6.11; N, 4.98; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 5H, **H2'', H3'', H4'', H5'', H6''**), 6.70 (s, 1H, **H1**), 6.61* (s, 1H, **H13**), 6.56 (s, 1H, **H10**), 6.54* (s, 1H, **H4**), 6.51* (s, 1H, **H2'**), 6.20 (dd, *J* = 15.5, 7.4 Hz, 1H, **H1'**), 6.06 (d, *J* = 7.5 Hz, 1H, **H9**), 5.87 (dd, *J* = 5.2, 1.5 Hz, 1H, **H15**), 4.76 (td, *J* = 4.0, 2.0 Hz, 1H, **H6**), 4.25 (ddd, *J* = 11.5, 4.9, 3.9 Hz, 1H, **H14a**), 3.92 (s, 3H, OC**H$_3$**), 3.85 (s, 3H, OC**H$_3$**), 3.83 (s, 3H, OC**H$_3$**), 3.76 (s, 3H, OC**H$_3$**) 3.21 (d, *J* = 3.9 Hz, 2H, **H5**), 2.81 (dd, *J* = 15.7, 3.7 Hz, 1H, **H14**), 2.59 (dd, *J* = 15.4, 11.8 Hz, 1H, **H14**), 2.12 (s, 3H, NCOC**H$_3$**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 168.0 (**C**O), 167.8 (**C**OCH_3), 149.5, 148.3, 148.0, 147.2 (4x**C**-OCH_3), 136.4 (**C1''**), 133.2 (**C2'**), 128.7 (**C3'', C5''**), 128.1, 127.7 (**C4'', C1'**), 126.8 (**C2'', C6''**), 125.2, 124.5, 123.6, 122.7 (**C4a, C9a, C13a, C15a**), 113.1 (**C1**), 111.5 (**C**H_{Ar}), 110.7, 110.4 (**C**H_{Ar}, **C10**), 56.5, 56.1, 56.0 (4xO**C**H_3) , 55.9 (**C6**), 54.5 (**C9**), 53.2 (**C14a**), 49.3 (**C15**), 32.6 (**C14**), 31.7 (**C5**), 20.6 (CO**C**H_3).

5.3.24.14. Synthesis of (6*S**,9*S**,14a*S**,15*R**,1'*E*)-2,3,11,12-tetramethoxy-16-(methylsulfonyl)-9-styryl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 36q.



Obtained according to the general procedure **5.3.24** using compound **26a** (0.10 g, 0.18 mmol), as starting material, cinnamadehyde (0.047 g, 0.36 mmol), *p*-toluenesulfinic acid (0.082 g, 0.54 mmol) and toluene (1.0 mL) as solvent. Purification by flash column chromatography on silica gel using 98:2 ethyl acetate: methanol as eluent afforded product **36q** (0.032 g, 0.054 mmol) as a brown solid in 30% yield; **Mp** 144–145 ºC; **IR (NaCl) ν_{max}** 3200, 2910cm^{-1}; **Analysis**: Calcd.for $C_{32}H_{34}N_2SO_7$: C, 65.07; H, 5.80; N, 4.74; S, 5.43. Found: C, 65.00; H, 5.71; N, 4.44; S, 5.36; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 3H, C**H**$_{Ar}$''), 7.23 – 7.10 (m, 2H, C**H**$_{Ar}$''), 6.75 – 6.57 (m, 4H, C**H**$_{Ar}$), 6.49 (d, *J* = 15.2 Hz, 1H, **H2'**), 6.28 (d, *J* = 15,5, 6.7 Hz, 1H, **H1'**), 6.15 (d, *J* = 6.7 Hz, 1H, **H9**), 5.08 (dd, *J* = 5.5, 1.8 Hz, 1H, **H15**), 4.88 – 4.76 (m, 1H, **H6**), 4.40 (ddd, *J* = 11.7, 5.3, 3.8 Hz, 1H, **H14a**), 3.94 (s, 3H. OC**H$_3$**), 3.88 – 3.85 (m, 6H, 2xOC**H$_3$**), 3.78 (s, 3H, OC**H$_3$**), 3.30 (dd, *J* = 17.4, 7.1 Hz, 1H, **H5**), 3.17 (dd, *J* = 17.4, 10.6 Hz, 1H, **H5**), 2.80 – 2.75 (m, 1H, **H14**), 2.75 (s, 3H, SO_2C**H$_3$**), 2.47 (dd, *J* = 15.4, 11.7 Hz, 1H, **H14**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 167.9 (**C**O), 149.8, 148.3, 148.1, 147.4 (4x**C**-OCH_3), 136.3 (**C1''**), 133.5 (**C2'**), 128.7 (**C3'', C5''**), 128.5 (**C4''**), 127.7 (**C1'**), 126.8 (**C2'', C6''**), 124.8, 124.4, 123.4, 121.8 (**C4a, C9a, C13a, C15a**), 112.4, 111.8, 110.7, 110.5 (**C**H$_{Ar}$), 56.5 (**C14a**), 56.2, 56.1, 56.1, 56.0 (4xO**C**H$_3$), 54.2, 54.1, 54.1 (**C6, C9, C15**), 40.7 (SO_2**C**H$_3$), 32.8 (**C14**), 29.8 (**C5**).

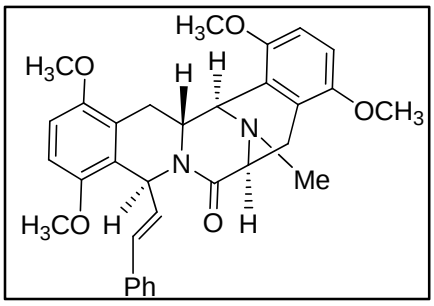
5.3.24.15. Synthesis of (6*S**,9*S**,14a*S**,15*R**,1'*E*)-1,4,10,13-tetramethoxy-16-methyl-9-styryl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 36r.



Obtained according to the general procedure **5.3.24** using compound **27b** (0.1 g, 0.12 mmol), as starting material, cinnamadehyde (0.064 g, 0.48 mmol), *p*-toluene sulfinic acid (0.112 g, 0.72 mmol) and toluene (1.0 mL) as solvent. Purification by flash column chromatography on silica gel using 90:10

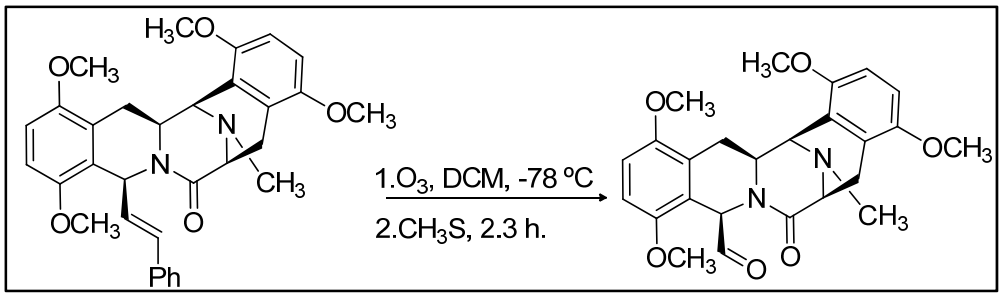
ethyl acetate:methanol as eluent afforded product **36r** (0.042 g, 0.079 mmol) as a brown solid in 33% yield; **Mp** 168–169 ºC; **IR (NaCl) ν_{max}** 2930, 1693, 1625 cm^{-1}; **Analysis**: Calcd.for $C_{32}H_{34}N_2O_5$: C, 72.98; H, 6.51; N, 5.32. Found: C, 72.79; H, 6.30; N, 5.40.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.36 – 7.13 (m, 5H, **H2'', H3'', H4'', H5'', H6''**), 6.70* (d, *J* = 4.0 Hz, 2H, **H11, H12**), 6.62* (d, *J* = 2.6 Hz, 2H, **H1, H2**), 6.51 (d, *J* = 5.4 Hz, 1H, **H9**), 6.41 (dd, *J* = 15.6, 5.4 Hz, 1H, **H1'**), 6.19 (d, *J* = 15.6 Hz, 1H, **H2'**), 4.56 (dd, *J* = 5.6, 0.9 Hz, 1H, **H15**), 4.41 – 4.26 (m, 1H, **H14a**), 3.88 (s, 3H, OCH_3), 3.86 – 3.79 (m, 1H, **H6**), 3.74 (s, 6H, 2xOCH_3), 3.68 (s, 3H, OCH_3), 3.17 (dd, *J* = 17.8, 4.4 Hz, 1H, **H14**), 3.00 – 2.91 (m, 2H, **H5**), 2.44 (s, 3H, N-CH_3), 2.06 (dd, *J* = 17.4, 12.3 Hz, 1H, **H14**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 171.1 (**C7**), 151.5, 151.3, 150.6 (3x**C**-OCH_3), 150.3 (**C10**), 137.1 (**C1''**), 131.6 (**C2'**), 128.4 (**C3'', C5''**), 127.7 (**C1'**), 127.4 (**C4''**), 126.7 (**C2'', C6''**), 124.0, 123.2, 123.1, 121.9 (**C4a, C9a, C13a, C15a**), 108.6, 108.2, 107.6, 107.6 (**C2, C3, C11, C12**), 58.8 (**C6**), 55.8, 55.7, 55.6, 55.3 (4xOCH_3), 53.3 (**C15**), 50.4 (**C14a**), 48.9 (**C9**), 40.3 (N-CH_3), 25.8 (**C14**), 22.9 (**C5**).

5.3.24.16. Synthesis of (6*S**,9*S**,14a*S**,15*R**,1'*E*)-1,4,10,13-tetramethoxy-16-methyl-9-styryl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 36s.



Obtained according to the general procedure **5.3.24** using compound **28b** (0.05 g, 0.12 mmol) as starting material, cinnamadehyde (0.032 g, 0.24 mmol), *p*-toluene sulfinic acid (0.056 g, 0.36 mmol) and toluene (1.0 mL) as solvent. Purification by flash column chromatography on silica gel using 9:1 ethyl acetate: methanol as eluent afforded product **36s** (0.045 g, 0.085 mmol) as a brown solid in 71% yield.; **Mp** 110–111 ºC; **IR (NaCl) ν_{max}** 2930, 1693, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{32}H_{34}N_2O_5$: C, 72.98; H, 6.51; N, 5.32. Found: C, 73.04; H, 6.62; N, 5.19.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.16 – 7.08 (m, 3H, **H3'',H4'', H5''**), 6.83 – 6.77* (m, 3H, **H2'', H6'', H3**), 6.72 – 6.63* (m, 3H, **H4, H11, H12**), 6.46 (bs, 1H, **H9**), 6.14 (dd, *J* = 16.3, 2.9 Hz, 1H, **H2''**), 5.19 (dd, *J* = 16.3, 2.1 Hz, 1H, **H1'**), 4.08 (s, 1H, **H15**), 3.83 (s, 3H, OCH_3), 3.83 – 3.81 (m, 10H, 3xOCH_3, **H14a**), 3.77 – 3.72 (m, 1H, **H6**), 3.59 (s, 3H, OCH_3), 3.28 (dd, *J* = 16.7, 11.9 Hz, 1H, **H5**), 3.05 – 2.88 (m, 3H, **H5, H14**), 2.45 (s, 3H, N-CH_3).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 151.4, 151.1, 151.1, 150.4 (**C7**, 4x**C**-OCH_3), 137.1 (**C1''**), 128.9* (**C4a**), 128.0 (**C3'', C5''**), 127.8 (**C1'**), 127.5 (**C2'**), 126.9 (**C4''**), 126.4 (**C2'', C6''**), 125.5, 125.2, 125.1* (**C9a, C13a, C15a**), 108.3, 108.0, 107.8 (**C2, C3, C11, C12**), 59.0 (**C14a**), 55.8, 55.8, 55.8, 55.6 (4xOCH_3), 55.1 (**C15**), 54.0 (**C6**), 49.7 (**C9**), 39.7 (N-CH_3), 29.1 (**C14**), 20.1 (**C5**).

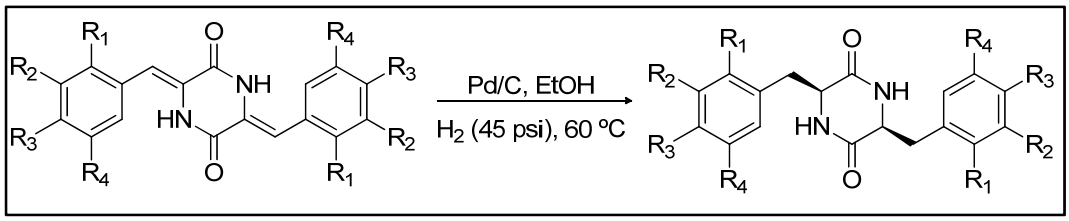
5.3.25. Synthesis of 1,4,10,13-tetramethoxy-7-oxo-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-9-carbaldehyde 37.



To a solution of **36r** (0.050 g, 0.094 mmol) in DCM (2.0 mL) at -78 ºC, an O_3 stream (0.4 bar of O_2) to flow 50 NL/h was bubbled during 5 minutes. The mixture was warmed to room temperature followed by the addition of CH_3S 0.2 mL. The reaction was stirred for 2.5 h. The crude was extracted with DMC (2x 20 mL), dried over anhydrous Na_2SO_4, filtered concentrated under pressure, and purified by flash column chromatography using a mixture of 9:1 ethyl acetate:methanol as eluent to obtain **37** (0.028 g, 0.062 mmol) as a unstable brown oil in 65% yield. **IR (NaCl)** ν_{max} 3200, 2930, 1860, 1693, 1625 cm^{-1}; **Analysis**: Calcd. for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39 Found: C, 65.55; H, 6.00; N, 6.40; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 9.68 (s, 1H, **C1'**), 6.66 – 6.53 (m, 4H, **H2, H3, H11, H12**), 6.33 (s, 1H, **H9**), 4.48 (d, *J* = 5.2 Hz, 1H, **H15**), 4.11 (dd, *J* = 10.7, 4.8 Hz, 1H, **H14a**), 3.80 (s, 0.4H, OC**H$_3$**), 3.80 (s, 2.7H, OC**H$_3$**), 3.73 (s, 2,5H, OC**H$_3$**), 3.71 (s, 0.6H, OC**H$_3$**), 3.68 – 3.65 (m, 6H, 2xOC**H$_3$**), 3.11 (dd, *J* = 17.7, 4.1 Hz, 1H, **H14**), 2.92 (m, 2H, **H5**), 2.64 (s, 2H), 1.92 (dd, *J* = 17.0, 10.4 Hz, 1H, **H14**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 195.3 (**C1'**), 166.8, 165.0 (**C7**), 153.6, 152.1 (2xOCH_3), 151.5, 151.5 (**C10**), 149.7 (OCH_3), 124.2, 123.7, 116.8, 116.6 (**C4a, C9a, C13a, C15a**), 114.0, 111.8, 109.7, 109.6, 108.6, 108.2 **(C2, C3, C11, C12**), 59.2, 58.5 (**C9**), 55.9, 55.9, 55.9, 55.8, 55.8 (4xO**C**H_3, **C6**), 55.3 (**C15**), 52.9 (**C14a**), 52.2 (NCH_3), 35.2 (**C14**), 27.3 (**C5**).

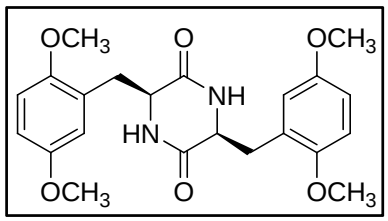
5.4. Synthesis of system (±)-(6S*,9S*,14aS*,15R*)-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one. Strategy core ACE-B-D.

5.4.1. General process to obtain of 3,6-bisbenzylpiperazine-2,5-dione 38a – 38b.



To a solution of **19** or **18b** (1.0 eq) in EtOH (60-110 mL), under argon atmosphere was added C/Pd 10% *w/w* (50% *w/w*), and H_2 (45 psi) at 60 ºC for and the reaction was stirred for 12 h. The crude was filtered through celite to remove the C/Pd and the celite was washed with DCM (3x 30 mL) for extract compound **38a–38b**. The organic layer was washed with saturated solution of $NaHCO_2$ and extracted with DCM (2x 10 mL) was dried over anhydrous Na_2SO_4, was filtered and was concentrated *in vacuo* to obtain **38a–38b.**

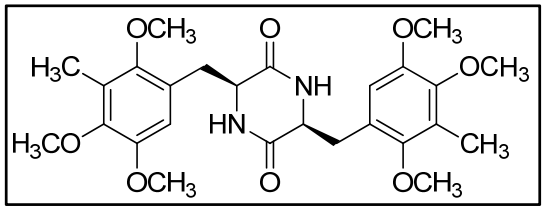
5.4.1.1. Synthesis of 3,6-bis(2,5-dimethoxybenzyl)piperazine-2,5-dione 38a.



Obtained according to the general procedure **4.3.1** using compound **18b** (1.00 g, 0.23 mmol) as starting material, Pd/C (0.50 g), and EtOH (60 mL) as solvent. Compound **38a** (0.98 g, 0.23 mmol) was obtained as a white solid 99% yield.; **Mp** 165–166 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis**: Calcd.for $C_{22}H_{26}N_2O_6$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.80; H, 6.35 N, 6.58; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.80 – 6.68 (m, 4H, **H3'', H4''**), 6.70 (d, *J* = 2.1 Hz, 1H, **H6''**), 6.03 (s, 2H, 2 x N**H**), 4.23 (dd, *J* = 8.7, 3.8 Hz, 2H, **H3, H6**), 3.79 (s, 6H, OC**H$_3$**), 3.76 (s, 6H, OC**H$_3$**), 3.37* (dd, *J* = 13.7, 3.8 Hz, 2H, C**H$_2$**-C3), 2.49* (dd, *J* = 13.7, 8.8 Hz, 2H, C**H$_2$**-C6).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ δ 167.6 (**C1, C4**), 153.8, 151.9 (2 x **C2''**, 2 x **C5''**), 125.1 (2 x

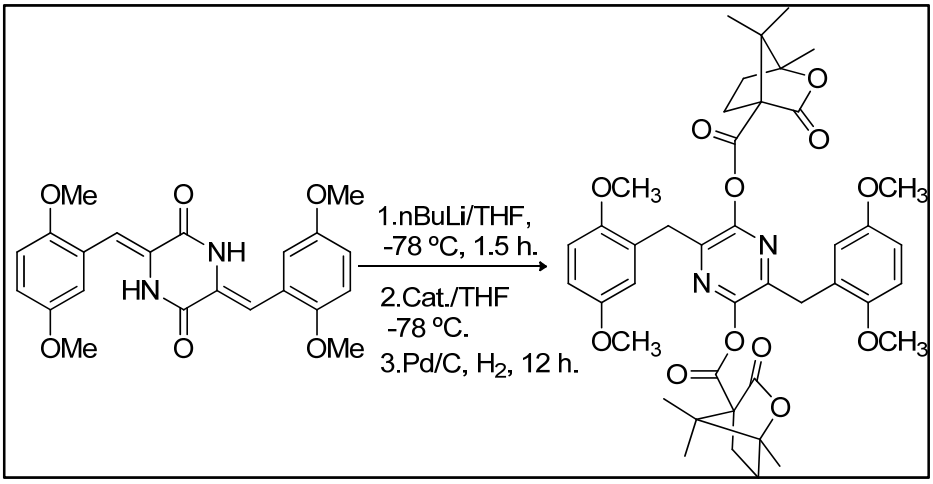
C1''), 118.0 (2 x **C6''**), 113.0, 111.7 (2 x **C3''**, 2 x **C4''**), 56.0, 55.8 (4 x O**C**H_3), 55.1 (**C3, C6**), 34.1 (2 x **C1'**).

5.4.1.2. Synthesis of 3,6-bis(2,4,5-trimethoxy-3-methylbenzyl)piperazine-2,5-dione 38b.



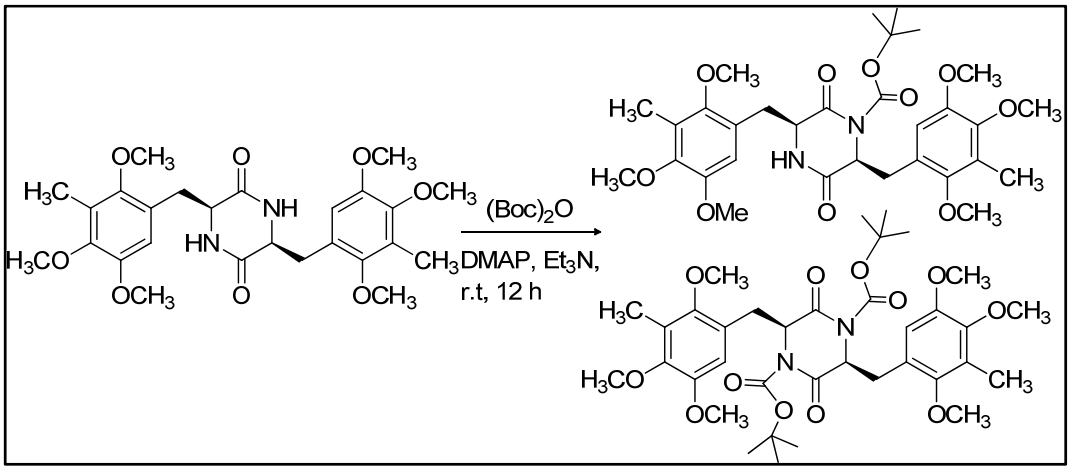
Obtained according to the general procedure **4.3.1** using compound **19** (2.00 g, 4.0 mmol) as starting material Pd/C (1.00 g), and EtOH (110 mL) as solvent the compound **38b** (2.05 g, 3.99 mmol) was obtained as a white solid 99% yield; **Mp** 194–195 ºC; **IR (NaCl) ν_{max}** 2938, 2360 cm^{-1}; **Analysis**: Calcd.for $C_{26}H_{34}N_2O_8$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.10; H, 6.76; N, 5.41; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.57 (s, 2H, C**H**$_{Ar}$), 6.54 (br. s, 2H, N**H**), 4.16 (dd, *J* = 9.0, 3.3 Hz, 2H, **H3, H6**), 3.81 (s, 6H, 2 x OC**H$_3$**), 3.77 (s, 6H, 2 x OC**H$_3$**), 3.67 (s, 6H, 2 x OC**H$_3$**), 3.30 (dd, *J* = 14.0, 3.4 Hz, 2H, C**H$_2$**-C3, C**H$_2$**-C6), 2.73 (dd, *J* = 14.0, 9.2 Hz, 2H, C**H$_2$**-C3, C**H$_2$**-C6), 2.20 (s, 6H, 2 x **CH$_3$**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 168.3 (**C1, C4**), 150.9, 149.7, 147.4 (6 x **C**-OCH$_3$), 126.1, 124.0 (2 x **C**-Me), 111.8 (2 x C**H**$_{Ar}$), 60.7, 60.3, 56.1 (6 x OCH$_3$), 55.8 (**C3, C6**), 32.9 (2 x **C**H$_2$), 9.8 (2 x **C**H$_3$).

5.4.2. Synthesis of (1'*S**, 4'*R**)-3,6-bis(2,5-dimethoxybenzyl)-2,5-bis((1,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-4-carbonyl)oxy)pyrazine 39.



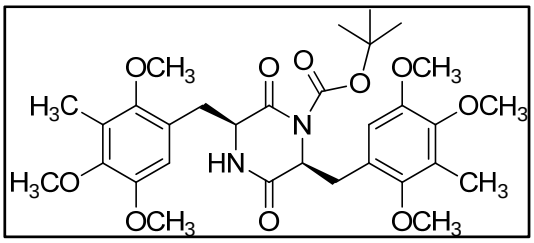
A solution of **18b** (0.30 g, 0.69 mmol) in dry THF (15 mL) at -78 ºC, 1.6 M *n*BuLi (0.96 mL, 1.52 mmol) was added and stirred for 1.5 h. Then, to the deep red solution, a solution of (1*S*)-(-)-camphanic chloride (0.3 g, 2.07 mmol) in dry THF (15 mL) at -78 ºC was added. The reaction was stirred for 8 h, and then 10% Pd/C (0.20 g) was added and the reaction was carried out under H_2 atmosphere (40 psi) at 60 ºC for 12 h. The mixture was filtered through celite for removed the Pd/C and the celite was washed with DCM (3 x 30 mL) to extract compound **39**. The solution was extracted with DCM (2x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to obtain **39** (0.1 g, 0.13 mmol) as a white solid in 19 % yield; **Mp** 156–157 ºC; **IR (NaCl) ν_{max}** 2930, 1783, 1720 cm^{-1}; **Analysis**: Calcd.for $C_{42}H_{48}N_2O_{12}$: C, 65.27; H, 6.26; N, 3.62. Found: C, 65.06; H, 6.20; N, 3.65; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.77 – 6.77 (m, 4H, **H3'''**, **H4'''**), 6.67 (d, *J* = 1.4 Hz, 2H, **H6'''**), 4.04 (s, 2H, **H1''**), 3.70 (s, 6H, 2xOC**H$_3$**), 3.66 (s, 6H, 2xOC**H$_3$**), 2.46* (ddd, *J* = 14.6, 10.7, 4.3 Hz, 2H, **H5**), 2.11* (ddd, *J* = 13.6, 8.5, 3.8 Hz, 2H, **H6**), 1.95* (ddd, *J* = 15.0, 10.7, 4.5 Hz, 2H, **H5**), 1.72* (ddd, *J* = 13.3, 9.3, 4.2 Hz, 2H, **H6**), 1.13 (s, 3H, C**H$_3$**-C1), 1.03 (s, 3H, C**H$_3$**-C7), 0.97 (s, 3H, C**H$_3$**-C7).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 177.9 (**C**OO-C4), 165.3 (**C3**), 153.5 (**C2'''**), 151.6 (**C3'''**), 150.3 (**C3', C6'**), 145.0 (**C2', C5'**), 126.2 (**C1'''**), 116.6 (**C6'''**), 112.8, 111.5 (**C3'''**, **C4'''**), 90.7 (**C1**), 56.0, 55.8 (4xOC**H$_3$**), 55.2, 55.1 (**C4**, **C7**), 32.8 (**C1''**), 30.5, 29.1 (**C5, C6**), 16.7, 16.6 (4x**C**H$_3$-C7), 9.8 (2x**C**H$_3$-C1).

5.4.3. General procedure to obtain (±)-1-*tert*-butyloxycarbonil- and (±)-1,4-di*tert*-butyloxycarbonil-3,6-bis(2,4,5-trimethoxy-3-methylbenzyl)piperazine-2,5-dione 40 and 41.



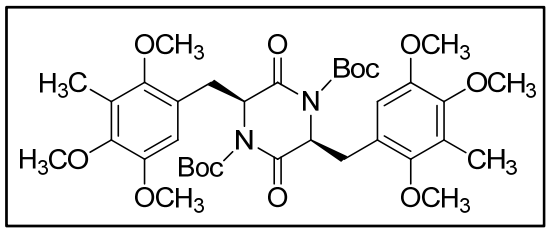
To a solution of **38b** (1.1 g, 2.15 mmol), $(Boc)_2O$ (0.47 g, 2.15 mmol), DMAP (0.28 g, 2.15 mmol) and Et_3N (0.32 mL, 2.15 mmol) in anhydrous DCM (4.0 mL) was added and stirred for 12 h at room temperature. The reaction was quenched with a saturated solution of NH_4Cl, extracted with DCM (2x 20 mL), and the organic layer was dried over anhydrous Na_2SO_4 and filtered. The solution was concentrated *in vaccuo* and purified by flash column chromatography using a mixture of diethyl ether:ethyl acetate as eluent to obtain compounds **40–41**.

5.4.3.1. Synthesis of (±)-1-*tert*-butyloxycarbonil-3,6-bis(2,4,5-trimethoxy-3-methylbenzyl)piperazine-2,5-dione 40.



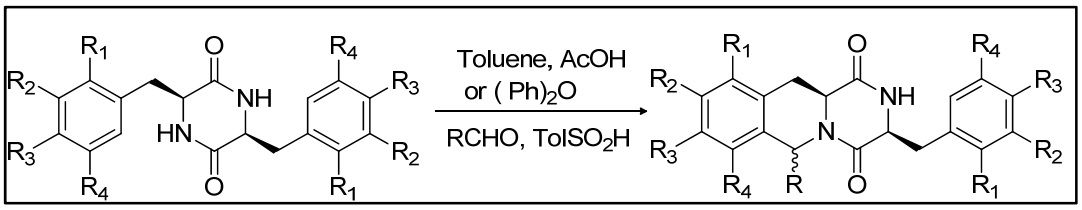
Obtained according to the general procedure **4.3.3** using compound **38b** (0.59 g, 1.14 mmol) as starting material, DMAP (0.14 g, 1.14 mmol), $(Boc)_2O$ (0.25 g, 1.14 mmol) and anhydrous DCM (2.0 mL) as solvent. Purification by flash column chromatography on silica gel using a mixture of 8:2 diethyl ether: ethyl acetate as eluent afforded product **40** (0.094 g, 0.15 mmol) as a brown oil in 13% yield; **IR (NaCl) ν_{max}** 2934, 2350, 1695 cm^{-1}; **Analysis**: Calcd.for $C_{31}H_{42}N_2O_{10}$: C, 61.77; H, 7.00; N, 4.68. Found: C, 61.78; H, 7.02; N, 4.65; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.46 (s, 1H, C**H**$_{Ar}$), 6.35 (s, 1H, C**H**$_{Ar}$), 5.80 (s, 1H, N**H**), 4.94 (t, *J* = 5.0 Hz, 1H, **H3**), 4.29 (dt, *J* = 10.0, 1.9 Hz, 1H, **H6**), 3.84 (s, 3H, OC**H$_3$**), 3.82 (s, 3H, OC**H$_3$**), 3.75 (s, 3H, OC**H$_3$**), 3.72 (s, 3H, OC**H$_3$**), 3.65 (s, 3H, OC**H$_3$**), 3.61 (s, 3H, OC**H$_3$**), 3.46 (dd, *J* = 13.7, 5.3 Hz, 1H, C**H$_2$**-C3), 3.15 (d, *J* = 13.8 Hz, 1H, C**H$_2$**-C3), 3.14 (dd, *J* = 13.6, 1.9 Hz, 1H, C**H$_2$**-C6), 2.21 (s, 3H, C**H$_3$**-C$_{Ar}$), 2.14 (s, 3H, C**H$_3$**-C$_{Ar}$), 1.51 (s, 9H, COC(C**H$_3$**)$_3$), 1.50 – 1.41 (m, 1H, C**H$_2$**-C6).; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.7, 166.1 (**C1, C4**), 151.9, 151.0, 150.9, 149.7, 149.4, 147.8, 147.5 (6x**C**-OCH_3, O**C**OC$(CH_3)_3$), 126.3, 126.1, 123.8, 123.3 (2x**C$_{Ar}$**, 2x**C$_{Ar}$**-CH_3), 113.1, 112.3 (**CH$_{Ar}$**), 84.1 (OCO**C**$(CH_3)_3$), 60.7, 60.6, 60.3, 60.3 (4xO**C**H_3), 59.6 (**C3**), 57.1, 56.3 (2xO**C**H_3), 56.2(**C6**, O**C**H_3), 36.4 (**C**H_2-C6), 33.9 (**C**H_2-C3), 28.0 (COC(**C**H_3)$_3$), 10.0, 9.7 (**C**H_3-C$_{Ar}$).

5.4.3.2. Synthesis of (±)-1,4-di*tert*-butyloxycarbonil-3,6-bis(2,4,5-trimethoxy-3-methylbenzyl)piperazine-2,5-dione 41.



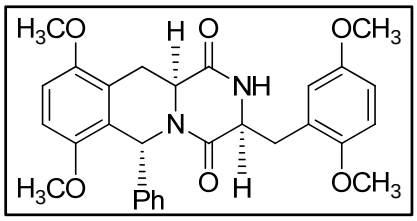
Obtained according to the general procedure **4.3.3** using compound **38b** (0.59 g, 1.14 mmol) as starting material DMAP (0.14 g, 1.14 mmol), $(Boc)_2O$ (0.25 g, 1.14 mmol) and dry DCM (2.0 mL) as solvent. Purification by flash column chromatography on silica gel using 5:5 petroleum ether:diethyl ether as eluent afforded product **41** (0.28 g, 0.40 mmol) as a brown oil in 35% yield.; **IR(NaCl) ν_{max}** 2936, 2360, 1683, 1488 cm^{-1}; **Analysis**: Calcd.for $C_{36}H_{50}N_2O_{12}$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.50; H, 7.05; N, 4.06; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.58 (s, 2H, CH_{Ar}), 5.17 (dd, *J* = 8.9, 5.1 Hz, 2H, **H3, H6**), 3.80, 3.69, 3.66 (s, 18H, 6xOCH_3) , 3.34* (dd, *J* = 13.6, 5.2 Hz, 2H, CH_2-C3), 2.78* (dd, *J* = 13.6, 9.0 Hz, 2H, CH_2-C6), 2.14 (s, 6H, 2xCH_3), 1.28 (s, 18H, 2xC-(CH_3)$_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 167.2 (**C1, C4**), 151.2, 149.6, 149.2, 147.3 (6x **C**-OCH_3, 2x**C**O-O^{t}Bu), 125.5, 123.6 (2xC_{Ar}, 2x**C**-Me), 111.7 (2xCH_{Ar}), 84.2 (2x**C**(CH_3)$_3$), 60.6, 60.1, 55.9 (6xOCH_3), 35.1 (2xCH_2-C3), 27.6 (2xC-(CH_3)$_3$), 9.7 (2xCH_3).

5.4.3.3. General procedure to obtain 3-benzyl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones 42a – 43b.



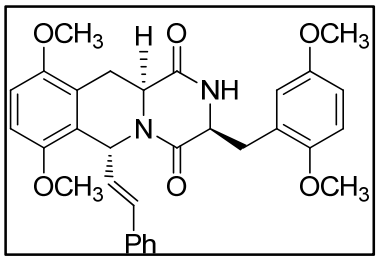
To a solution of **37** (1.00 eq) in dry toluene, acetic acid or $(PhO)_2O$, *p*-toluenesulfinic acid (1.00 – 1.10 eq) and the corresponding aryl aldehyde (1.00 – 1.05 eq) were added at 110–120 ºC and the reaction was stirred for 3–12 h. The reaction was quenched with a saturated solution of $NaHCO_3$, extracted with DCM (2x 20 mL), and the organic layer was dried over anhydrous Na_2SO_4 and filtered. The solution was concentrated under reduced pressure and purified by flash column chromatography using a mixture of diethyl ether:ethyl acetate as eluent to obtain **42a–43b**.

5.4.3.4. Synthesis of (3*S**,6*S**,11a*S**)-3-(2,5-dimethoxybenzyl)-7,10-dimethoxy-6-phenyl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 42a.



Obtained according to the general procedure **4.3.3** using compound **38a** (0.10 g, 0.23 mmol) as starting material, *p*-toluene sulfinic acid (0.040 g, 0.23 mmol), benzaldehyde (0.050 mL, 0.49 mmol) and acetic acid (2.0 mL) as solvent at 120 ºC for 12 h. Purification by flash column chromatography on silica gel using 5:5 diethyl ether: ethyl acetate as eluent afforded product **42a** (0.072 g, 0.14 mmol) as a brown solid in 65% yield; **Mp** 198–199 ºC; **IR (NaCl) ν_{max}** 3210, 2900, 1893, 1625 cm^{-1}; **Analysis**: Calcd for $C_{29}H_{30}N_2O_6$: C, 69.31; H, 6.02; N, 5.57. Found: C, 69.46; H, 6.06; N, 5.50; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.26 – 7.17 (m, 3H, **H3',H4', H5'**), 7.14 (s, 1H, **H6**), 7.13 – 7.03 (m, 2H, **H2',H6'**), 6.81 – 6.65 (m, 4H, **H8, H9, H3'', H4''**), 6.49 (d, *J* = 2.9 Hz, 1H, **H6''**), 6.25 (bs, 1H, N**H**), 4.43 (dd, *J* = 4.3, 2.8 Hz, 1H, **H11a**), 3.92 (dd, *J* = 12.7, 5.2 Hz, 1H, **H3**), 3.79 – 3.59 (m, 9H, 3xOC**H$_3$**), 3.38 (dd, *J* = 13.5, 5.0 Hz, 1H, C**H$_2$**-C3), 3.23 (s, 3H, OC**H$_3$**), 3.13 – 2.62 (m, 2H, C**H$_2$**-C3, **H11**), 1.41 (dd, *J* = 17.3, 12.8 Hz, 1H, **H11**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 167.4 (**C1**), 163.5 (**C4**), 153.6, 152.1, 151.2 (3x**C**-OCH_3), 150.3 (**C7**), 140.1 (**C1'**), 128.5 (**C3', C5'**), 128.3 (**C2', C6'**), 127.8 (**C4'**), 124.2, 123.5, 123.3 (**C1'', C6a, C10a**), 115.8 (**C6''**), 114.6, 112.1, 108.7, 108.2 (**C8, C9, C3'', C4''**), 56.5 (**C11a**), 56.0, 55.9, 55.6, 55.2 (4xOCH_3), 51.1 (**C6**), 50.3 (**C3**), 35.2 (CH_2-C3), 28.3 (**C11**).

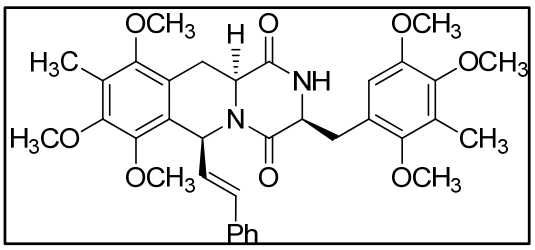
5.4.3.5. Synthesis of (3*S**,6*R**,11a*S**,*E*)-3-(2,5-dimethoxybenzyl)-7,10-dimethoxy-6-styryl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 42b.



Obtained according to the general procedure **4.3.3** using compound **38a** (0.20 g, 0.47 mmol) as starting material, *p*-toluene sulfinic acid (0.11 g, 0.71 mmol), cinnamaldehyde (0.1 mL, 0.79 mmol) and $(Ph)_2O$ (1.60 mL) as solvent at 120 ºC for 12 h. Purification by flash column chromatography on silica gel using 5:5 diethyl ether: ethyl acetate as eluent afforded product **42b** (0.17 g, 0.31 mmol) as a brown solid in 65% yield; **Mp** 104–105 ºC; **IR (NaCl) ν_{max}** 3100, 2920,

1613, 1600 cm^{-1}; **Analysis**: Calcd.for $C_{31}H_{32}N_2O_6$: C, 70.44; H, 6.10; N, 5.30. Found: C, 70.49; H, 6.11; N, 5.20; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H, **H2'' - H6''**), 6.82 – 6.67 (m, 5H, **H8, H9, H3''', H4''',** N**H**), 6.66 (d, *J* = 3.9 Hz, 1H, **H6**), 6.54 (s, 1H, **H6'''**), 6.33 (dd, *J* = 16.5, 3.6 Hz, 1H, **H1'**), 6.19 (d, *J* = 16.1 Hz, 1H, **H2'**), 4.51 (t, *J* = 4.7 Hz, 1H, **H3**), 4.29 (dd, *J* = 12.0, 4.5 Hz, 1H, **H11a**), 3.85 – 3.68 (m, 9H, 3xO**C**H_3), 3.41 (dd, *J* = 13.3, 4.3 Hz, 1H, C**H_2**-C3), 3.29 (s, 3H, O**C**H_3), 3.21 – 2.99 (m, 2H, C**H_2**-C3, **H11**), 1.41 (dd, *J* = 18.3, 13.5 Hz, 1H, **H11**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 167.7 (**C1**), 163.6 (**C4**), 153.4, 152.1, 151.1, 150.1 (4x**C**-OCH$_3$), 136.4 (**C1''**), 132.7 (**C2'**), 128.5* (**C2'', C6''**), 127.8 (**C4''**), 126.6* (**C3'', C5''**), 126.5 (**C1'**), 124.1, 123.1 (**C1''', C6a, C10a**), 116.0 (**C6'''**), 114.4, 111.8, 108.6, 108.0 (**C8, C9, C3''', C4'''**), 56.4 (**C3**), 55.8, 55.6, 55.5, 55.1 (4xO**C**H_3), 50.5 (**C11a**), 49.2 (**C6**), 35.0 (CH_2-C3), 28.1 (**C11**).

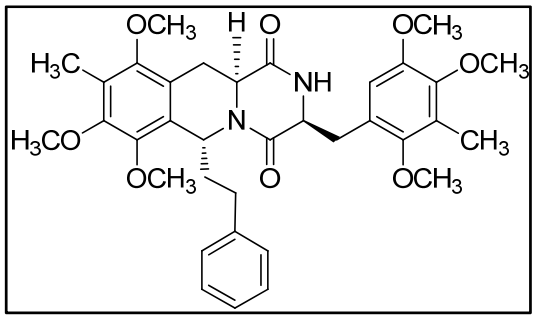
5.4.3.6. Synthesis of (3*S**,6*S**,11a*S**,*E*)-7,8,10-trimethoxy-9-methyl-3-(2,4,5-trimethoxy-3-methylbenzyl)- 6-styryl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione43a.



Obtained according to the general procedure **4.3.3** using compound **38b** (0.60 g, 1.20 mmol) as starting material, *p*-toluene sulfinic acid (0.21 g, 1.32 mmol), cinnamaldehyde (0.17 g, 1.26 mmol) and toluene (6.0 mL) as solvent at 115 ºC for 5.5 h. Purification by flash column chromatography on silica gel using 5:5 diethyl ether:ethyl acetate as eluent afforded product **43a** (0.30 g, 0.48 mmol) as a brown solid in 40% yield; **Mp** 107–109ºC; **IR (NaCl) ν_{max}** 2981, 2838, 2360, 1594 cm^{-1}; **Analysis**: Calcd.for $C_{35}H_{40}N_2O_8$: C, 68.17; H, 6.54; N, 4.54. Found: C, 68.09; H, 6.44; N, 4.59; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.29- 7.21 (m, 5H, **H2'' - H6''**), 6.61 (b.d, *J* = 4.9 Hz, 1H, **H6**), 6.44 (s, 1H, C**H**$_{Ar}$), 6.41 (d, *J* = 1.5 Hz, 1H, N**H**), 6.32 (dd, *J* = 15.9, 5.0 Hz, 1H, **H1'**), 6.20 (d, *J* = 16.0 Hz, 1H, **H2'**), 4.44 (b.t, *J* = 4.0 Hz, 1H, **H3**), 4.24 (dd, *J* = 11.8, 4.7 Hz, 1H, **H11a**), 3.79 (s, 3H, C**H$_3$**O-C7), 3.78 (s, 3H, OC**H$_3$**), 3.69(s, 3H, OC**H$_3$**), 3.64 (s, 3H, C10-OC**H$_3$**), 3.62 (s, 3H, OC**H$_3$**), 3.44 (s, 3H, C8-OC**H$_3$**), 3.24 (dd, *J* = 13.7, 4.4 Hz, 1H, C**H$_2$**-C3), 3.19 (dd, *J* = 16.9, 4.8 Hz, 1H, **H11),** 3.04 (dd, *J* = 13.7, 6.2 Hz, 3H, C**H$_2$**-C3), 2.19 (s,3H, C**H$_3$**), 2.17 (s,3H, C**H$_3$**-C9), 1.91 (dd, *J* = 16.9, 11.9 Hz, 1H, **H11**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 167.1 (**C1**), 163.8 (**C4**), 152.3 (**C**-OCH$_3$), 151.5 (**C10**), 150.3 (**C**-OCH$_3$), 149.4 (**C8**), 147.4 (**C**-OCH$_3$), 146.1 (**C7**), 136.1 (**C1''**), 133.4 (**C2'**) 128.6 (**C3'',C5''**), 128.1 (**C4''**) , 127.0 (**C1'**), 126.7 (**C2'',C6''**), 126.0 (**C9**), 125.1, 124.9 (**C6a, C**-Ar), 123.1 (**C**-Me) , 121.7 (**C10a**), 111.2

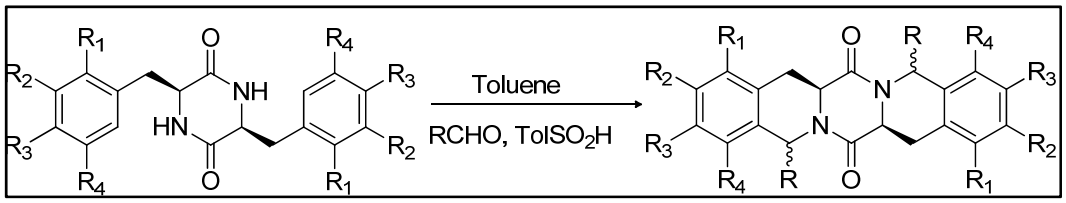
(**C**H_{Ar}), 60.7, 60.3, 60.3, 60.2, 60.0 (5x**O**CH_3), 56.5 (**C3**), 55.5 (**O**CH_3), 51.1 (**C11a**), 49.6 (**C6**), 35.1 (CH_2-C3), 28.0 (**C11**), 9.9, 9.5 (2x**C**H_3).

5.4.3.7. Synthesis of (±)-(3*S**,6*R**,11a*S**,*E*)-7,8,10-trimethoxy-9-methyl-6-phenethyl-3-(2,4,5-trimethoxy-3-methylbenzyl)-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 43b.



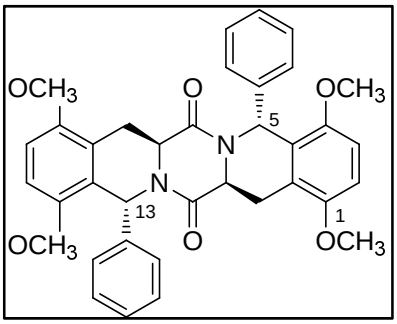
Obtained according to the general procedure **4.3.3** using compound **38b** (0.60 g, 1.20 mmol) as starting material, *p*-toluene sulfinic acid (0.21 g, 1.32 mmol), cinnamaldehyde (0.16 g, 1.26 mmol) and toluene (6.0 mL) as solvent at 115 ºC for 48 h. Purification by flash column chromatography on silica gel using 5:5 diethyl ether:ethyl acetate as eluent afforded product **43b** (0.15 g, 0.24 mmol) as a brown solid in 20% yield; **Mp** 125–127 ºC; **IR (NaCl) ν_{max}** 2937, 2360 cm^{-1}; **Analysis**: Calcd.for $C_{35}H_{42}N_2O_8$: C, 67.94; H, 6.84; N, 4.53. Found: C, 67.86; H, 6.81; N, 4.41; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.29 – 7.27 (m, 1H, **H4''**), 7.25 – 7.18 (m, 4H, **H2'', H3'' , H5'', H6''**), 6.66 (s, 1H, C**H**$_{Ar}$), 6.55 (s, 1H, N**H**), 5.89 (dd, *J* = 11.0, 2.8 Hz, 1H, **H6**), 4.36 – 4.20 (m, 2H, **H11a, H3**), 3.79 (s, 3H, OC**H**$_3$), 3.77 (s, 3H, OC**H**$_3$), 3.76 (s, 3H, OC**H**$_3$), 3.74 (s, 3H, OC**H**$_3$), 3.72 (s, 3H, OC**H**$_3$), 3.63 (s, 3H, OC**H**$_3$), 3.54 – 3.39 (m, 2H, C**H**$_2$-C3, **H2'**), 3.33 (dd, *J* = 16.9, 4.5 Hz, 1H, **H11**), 3.03 (dd, *J* = 13.9, 8.1 Hz, 1H, C**H**$_2$-C3), 2.83 – 2.47 (m, 3H, **H11, H1', H2'**), 2.22 (s, 3H, C**H**$_3$), 2.15 (s, 3H, C**H**$_3$), 2.07 – 1.94. (m, 1H, **H1'**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 167.5, 165.0 (**C1, C4**), 152.4, 151.0, 150.6, 149.7, 147.5, 146.1 (6x**C**-OCH_3), 141.4 (**C1''**), 128.5** (**C3'',C5''**) 128.5* (**C1''**), 128.5** (**C2'',C6''**), 126.1* (**C6a**), 126.0 (**C4''**), 124.4, 123.8, 120.7* (2x **C**-CH_3, **C10a**), 111.8 (**C**H_{Ar}), 60.8, 60.4, 60.3, 60.2, 60.1, 56.0 (6x OCH_3), 55.6, 51.9 (**C3, C11a**), 49.4 (**C6**), 34.9, 33.6 (**C1',C2'**), 33.0 (CH_2-C3), 27.7 (**C11**), 9.9, 9.4 (2x**C**H_3).

5.4.4. General procedure to obtain of 7a,8,15a,16-tetrahydropyrazino[1,2-*b*:4,5-*b*']diisoquinoline-7,15(5*H*,13*H*)-dione 44–45.



To a solution of **38** (1.00 eq) in dry toluene, acetic acid or $(PhO)_2O$, *p*-toluenesulfinic acid (1.00 – 3.00 eq) and the corresponding aryl aldehyde (1.00 – 1.05 eq) were added at 120 ºC and the reaction was stirred for 3–12 h. The reaction was quenched with saturated solution of $NaHCO_3$, extracted with DCM (2x 20 mL), and the organic layer was dried over anhydrous Na_2SO_4 and filtered. The solution was concentrated under reduced pressure and purified by flash column chromatography using a mixture of diethyl ether:ethyl acetate as eluent to obtain **44–45**.

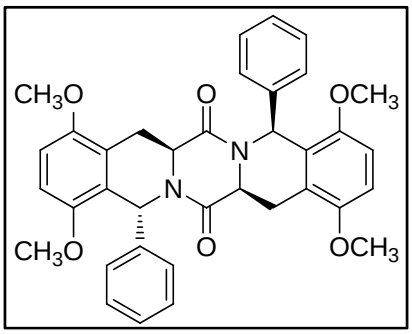
5.4.4.1. Synthesis of (±) (5*S**,13*S**)-1,4,9,12-tetramethoxy-5,13-diphenyl-7a,8,15a,16-tetrahydropyrazino[1,2-*b*:4,5-*b*']diisoquinoline-7,15(5*H*,13*H*)-dione 44a.



Obtained according to the general procedure **4.3.4** using compound **38a** (0.10 g, 0.23 mmol) as starting material, *p*-toluene sulfinic acid (0.080 g, 0.46 mmol), benzaldehyde (0.10 mL, 0.98 mmol) and AcOH (2.0 mL) as solvent at 120 ºC for 12 h. Purification by flash column chromatography on silica gel using 9:1 diethyl ether:ethyl acetate as eluent afforded product **44a** (0.052 g, 0.09 mmol) as a yellow solid in 37% yield; **Mp** 286–287 ºC; **IR (NaCl) ν_{max}** 2910, 1693, 1625 cm^{-1}; **Analysis**: Calcd.for $C_{36}H_{34}N_2O_6$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.40; H, 5.56; N, 4.64; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.25 – 7.23 (m, 6H, C**H$_{Ar}$**-C5, C**H$_{Ar}$**-C13), 7.14 – 7.09 (m, 4H, C**H$_{Ar}$**-C5, C**H$_{Ar}$**-C13), 7.07 (s, 2H, **H5, H13**), 6.79 – 6.67 (m, 4H**, H2, H3, H10, H11**), 4.23 (dd, *J* = 12.6, 4.7 Hz, 1H, **H7a, H15a**), 3.78 (s, 6H, 2xOC**H$_3$**), 3.57 (s, 6H, 2xOC**H$_3$**), 3.55 – 3.46 (m, 2H, **H8, H16**), 2.70 (dd, *J* = 17.6, 12.7 Hz, 2H, **H8, H16**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.34 (**C7, C15**), 151.4, 150.8 (4xC-OCH$_3$), 140.3 (**C1', **

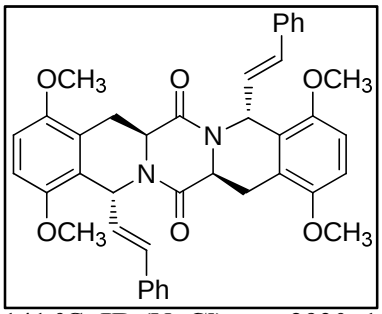
C1''), 128.8, 128.7 (**C2', C6', C3', C5'**, **C2'', C6'', C3'', C5''**), 128.1 (**C4', C4''**), 124.2, 123.5 (**C4a, C8a, C12a, C16a**), 109.1, 108.9 (**C2, C3, C10, C11**), 56.2, 56.0 (4xOCH_3), 51.5, 51.3 (**C5, C7a, C13, C15a**), 30.1 (**C8, C16**).

5.4.4.2. Synthesis of (±)-*trans*-(5*S**,13*R**)-1,4,9,12-tetramethoxy-5,13-diphenyl-7a,8,15a,16-tetrahydropyrazino[1,2-*b*:4,5-*b*']diisoquinoline-7,15(5*H*,13*H*)-dione 44b.



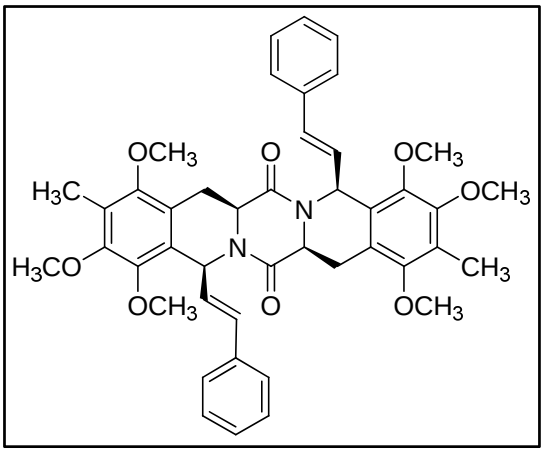
Obtained according to the general procedure **4.3.4** using compound **38a** (0.10 g, 0.23 mmol) as starting material *p*-toluene sulfinic acid (0.080 g, 0.46 mmol), benzaldehyde (0.10 mL, 0.98 mmol) and AcOH (2.0 mL) as solvent at 120 ºC for 12 h. Purification by flash column chromatography on silica gel using 9:1 diethyl ether:ethyl acetate as eluent afforded product **44b** (0.01 g, 0.016 mmol) as a yellow solid in 7% yield; **Mp** 262–263 ºC; **IR (NaCl) ν_{max}** 2910, 1693, 1625 cm^{-1}. **Analysis**: Calcd.for $C_{36}H_{34}N_2O_6$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.30; H, 5.66; N, 4.63; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.26 – 7.20 (m, 7H, C**H$_{Ar}$**-C5, C**H$_{Ar}$**-C13), 7.15* (s, 1H, **H5**), 7.14 – 7.08 (m, 3H, C**H$_{Ar}$**-C5, C**H$_{Ar}$**-C13), 7.07* (s, 1H, **H13**), 6.71 – 6.50 (m, 4H, **H2, H3, H10, H11**), 4.23** (dd, *J* =12.3, 4.8 Hz, 2H, **H7a**), 4.23** (dd, *J* =12.3, 4.8 Hz, 2H, **H15a**), 3.84 (s, 3H, OC**H$_3$**), 3.78 (s, 3H, OC**H$_3$**), 3.65 – 3.56# (m, 2H, **H8**), 3.57 (s, 6H, 2xOC**H$_3$**), 3.55 – 3.44# (m, 2H, **H16**), 2.84 – 2.57 (m, 4H).; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.1, 164.1 (**C7, C15**), 151.2, 151.1, 150.5, 150.4 (4xOCH_3), 140.8, 140.0 (**C1'', C1'''**), 128.6, 128.5, 128.4, 128.0 (**C2', C3', C5', C6', C2'', C3'', C5'', C6''**), 127.9, 127.8 (**C4', C4''**), 123.9, 123.4, 123.3, 123.3 (**C4a, C8a, C12a, C16a**), 108.9, 108.8, 108.6, 108.5 (**C2, C3, C10, C11**), 55.9, 55.8, 55.7 (4xOCH_3), 51.2, 51.1 (**C5, C13**), 50.8, 50.5 (**C7a, C15a**), 29.9, 29.8 (**C8, C16**).

5.4.4.3. Synthesis of (±)-(5*S**,13*R**,*1'E,1'''E*)-1,4,9,12-tetramethoxy-5,13-distyryl-7a,8,15a,16-tetrahydropyrazino[1,2-*b*:4,5-*b*']diisoquinoline-7,15(5*H*,13*H*)-dione **44c**.



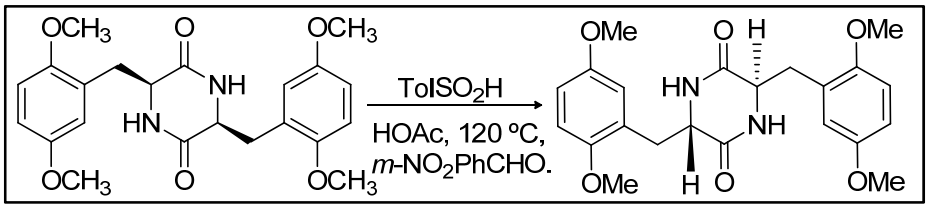
Obtained according to the general procedure **4.3.4** using compound **38a** (0.20 g, 0.46 mmol) as starting material *p*-toluene sulfinic acid (0.21 g, 1.33 mmol), cinnamaldehyde (0.2 mL) and toluene (1.0 mL) as solvent at 120 ºC for 12 h. Purification by flash column chromatography on silica gel using 5:5 diethyl ether:ethyl acetate as eluent afforded product **44c** (0.242 g, 0.37 mmol) as a brown solid in 80% yield; **Mp** 140–141 ºC; **IR (NaCl) ν_{max}** 2930, 1693, 1625 cm^{-1}; **Analysis**: Calcd.for $C_{40}H_{38}N_2O_6$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.70; H, 5.98; N, 4.30.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.31 – 7.20 (m, 10H, C**H$_{Ar}$**-C2', C**H$_{Ar}$**-C2'''), 6.73 (s, 4H, **H2, H3, H10, H11**), 6.61 (d, *J* = 4.7 Hz, 2H, **H5, H13**), 6.35 (dd, *J* = 16.0, 4.8 Hz, 2H, **H1', H1'''**), 6.19 (d, *J* = 16.0 Hz, 2H, **H2', H2'''**), 4.52 (dd, *J* = 12.5, 4.5 Hz, 2H, **H7a, H15a**), 3.75 (s, 6H, 2xOC**H$_3$**), 3.74 (s, 6H, 2xOC**H$_3$**), 3.50 (dd, *J* = 17.5, 4.6 Hz, 2H, **H8, H16**), 2.65 (dd, *J* = 17.5, 12.6 Hz, 2H, **H8, H16**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.1 (**C7**), 151.1, 150.4 (4x**C**-OCH_3), 136.5 (**C1'', C1^{IV}**), 133.1 (**C1', C1'''**), 128.6* (**C2'', C6'', C2^{IV}, C6^{IV}**), 127.9 (**C2', C2'''**), 126.7* (**C3'', C5'', C3^{IV}, C5^{IV}**),, 126.6 (**C4'', C4^{IV}**), 123.5, 122.9 (**C4a, C8a, C12a, C16a**), 108.7, 108.4 (**C2, C3, C10, C11**), 55.9, 55.6 (2xOCH_3), 51.5 (**C7a, C15a**), 49.4 (**C5, C13**), 29.8 (**C8, C16**).

5.4.4.4. Synthesis of (±)-(5R*,13*S**,*1'E,1'''E*)-1,3,4,9,11,12-hexamethoxy-2,10-dimethyl-5,13-distyryl-7a,8,15a,16-tetrahydropyrazino[1,2-*b*:4,5-*b'*]diisoquinoline-7,15(5*H*,13H)-dione 45.



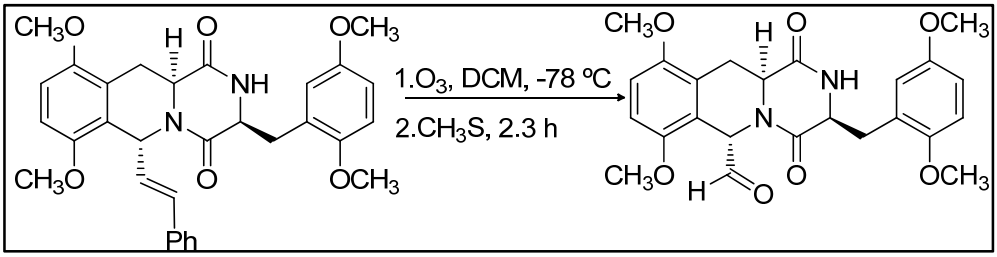
Obtained according to the general procedure **4.3.4** using compound **38b** (0.10 g, 0.193 mmol) as starting material, *p*-toluene sulfinic acid (0.045 g, 0.29 mmol), cinnamaldehyde (0.128 g, 0.96 mmol) and $(Ph)_2O$ (1.40 g) as solvent at 140 ºC for 6 h. Purification by flash column chromatography on silica gel using diethyl ether as eluent afforded product **45** (0.14 g, 0.19 mmol) as a brown solid in 99% yield; **Mp** 105–107ºC; **IR (NaCl)** ν_{max} 2938, 2359 cm^{-1}; **Analysis**: Calcd.for $C_{44}H_{46}N_2O_8$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.30; H, 6.32; N, 3.86; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 10H, C**H$_{Ar}$**), 6.61 (d, *J* = 5.1 Hz, 2H, **H5, H13**), 6.40 (dd, *J* = 15.9, 5.1 Hz, 2H, **H1', H1'''**), 6.27 (d, *J* = 16.0 Hz, 2H, **H2', H2'''**), 4.48 (dd, *J* = 12.5, 4.3 Hz, 2H, **H7a, H15a**), 3.81 (s, 6H, OC**H$_3$**), 3.80 (s, 6H, OC**H$_3$**), 3.68 (s, 6H, OC**H$_3$**), 3.54 (m, *J* = 16.9, 4.3 Hz, 2H, **H8, H16**), 2.72 (dd, *J* = 16.9, 12.6 Hz, 2H, **H8, H16**), 2.22 (s, 6H, C**H$_3$**-C2**,** C**H$_3$**-C10); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 163.9 (**C7, C15**), 152.3, 150.6, 146.5 (6xC-OCH_3), 136.2 (**C1'', C1^{IV}**), 133.9 (**C2', C2'''**), 128.7 (**C3'', C3^{IV}, C5'', C5^{IV}**), 128.2 (**C4'', C4^{IV}**), 127.0 (**C1', C1'''**), 126.8 (**C2'', C2^{IV}, C6'', C6^{IV}**), 125.2* (**C2, C10, C4a, C12a**), 121.8* (**C4a, C12a**), 60.3, 60.2, 60.1 (6xOCH_3), 51.65 (**C7a, C15a**), 49.8 (**C5, C13**), 9.6 (2xCH_3).

5.4.5. Synthesis of (±)-(3*R**,6*S**)-3,6-bis(2,5-dimethoxybenzyl)piperazine-2,5-dione 46.



To a solution of **38a** (0.20 g, 0.47 mmol) in acetic acid (4.5 mL), *p*-toluenesulfinic acid (0.073 g, 0.47 mmol) and *m*-nitrobenzaldehyde (0.27 g, 1,78 mmol) were added at 120 ºC and the reaction was stirred for 24 h. The reaction was quenched with saturated solution of Na_2HCO_3, extracted with DCM (2x 20 mL), and the organic layer was dried over anhydrous Na_2SO_4 and filtered. The solution was concentrated *in vacuo* and purified by flash column chromatography using a mixture of 8:2 diethyl ether:ethyl acetate as eluent to obtain **46** (0.11 g, 0.24 mmol) as a pale brown solid in 52% yield; **Mp** 168–169 ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis:** Calcd. for $C_{22}H_{26}N_2O_6$: C, 63.76; H, 6.32; N, 6.76 Found: C, 63.46; H, 6.36 ; N, 7.00; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.78 (d, *J* = 2.4 Hz, 4H, **H3'',H4'', H3''', H4'''**), 6.70 (s, 2H, **H6'', H6'''**), 6.03 (s, 2H, N**H**), 3.98 – 3.87 (m, 2H, **H3, H6**), 3.78 (s, 6H, 2xOC**H$_3$**), 3.71 (s, 6H, 2xOC**H$_3$**), 3.33 (dd, *J* = 13.6, 4.3 Hz, 2H, C**H**-C3, C**H**-C6), 2.85 (dd, *J* = 13.6, 8.1 Hz, 2H, C**H**-C3, C**H**-C6).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 168.0 (2x**C**NO), 153.8, 152.0 (4x**C**-OCH_3), 124.9 (**C1', C1''**), 117.4 (**C6', C6''**), 113.4, 111.7 (**C3', C3'', C4', C4''**), 56.0, 55.8 (4xO**C**H_3), 55.4 (**C3, C6**), 33.9 (**C**H_2).

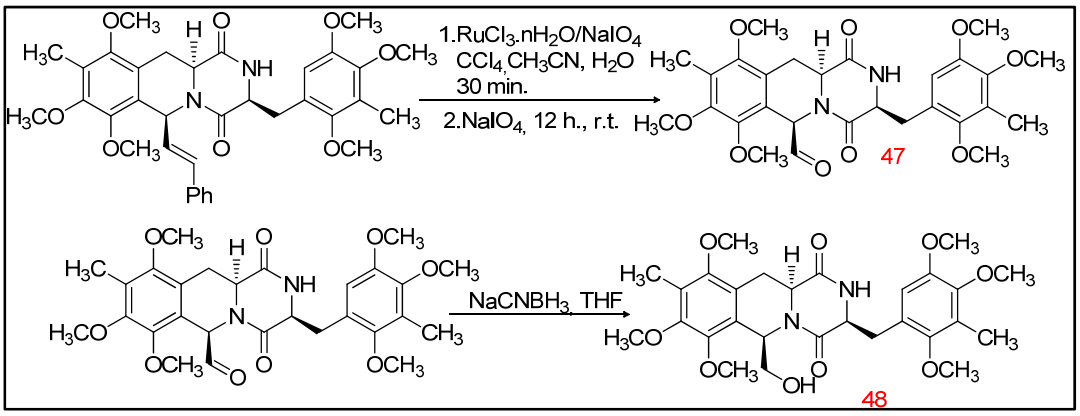
5.4.6. Synthesis of (±)-(3*S**,6*S**, *11aS**)-3-(2,5-dimethoxybenzyl)-7,10-dimethoxy-1,4-dioxo-2,3,4,6,11,11a-hexahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-6-carbaldehyde 47.



To a solution of **39b** (0.050 g, 0.077 mmol) in DCM (2.0 mL) at -78 ºC O_3 (0.4 bar of O_2) was added flowing 50 NL/h during 5 minutes. The mixture was warmed at room temperature and 0.2 mL of CH_3S was added during 2.5 h. The crude was extracted with DMC (2 x 20 mL), filtered, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography using a mixture of 8:2 diethyl ether:ethyl acetate as eluent to obtain **43** (0.028 g, 0.062 mmol) as a unstable brown oil in 80% yield as a mixture 1:1 of rotamers in $CDCl_3$, 25ºC; **IR (NaCl) ν_{max}** 2930, 1820**,** 1693, 1625 cm^{-1}; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 9.66 (s, 1H, **H1'**), 7.22 – 7.09* (m, 1.5H, **H8**), 6.81 – 6.56* (m, 4H**, H3'', H4'', H6'',**

NH, H9), 6.50 (s, 1H, **H6**), 6.27* (dd, *J* = 16.2, 3.8 Hz, 0.5H, **H4''**), 4.56 – 4.32 (m, 1H, **H3**), 4.32 – 4.17 (dd, *J* = 12.2, 4.2 Hz, 0.5H, **H11a**), 4.01 (dd, *J* = 12.2, 4.2 Hz, 0.5H, **H11a**), 3.88 – 3.67 (m, 9H, 3xOC**H**$_3$), 3.53 – 3.40 (m, 1H, C**H**$_2$-C3), 3.34 (s, 1.5H, OC**H**$_3$), 3.31 (s, 1.5H, OC**H**$_3$), 3.36 – 2.84 (m, 2H, C**H**$_2$-C3, **H11**), 1.71 – 1.26 (m, 1H, **H11**); ^{13}**C NMR** (63 MHz, $CDCl_3$) δ 195.3 (**C1'**), 167.7, 166.8, 164.9, 163.6* (**C1, C4**), 153.5, 152.3, 152.1, 151.4, 151.1, 150.1, 149.7 (4x**C**-OCH_3), 136.4, 132.8, 128.5, 127.8, 126.6, 126.5 (**C8, C9, C3'', C4''**), 124.2, 124.1, 123.6, 123.1 (**C6a, C10a, C1''**), 116.7, 116.6 (**C6''**), 116.0, 114.4, 114.0, 111.9, 111.8, 109.6, 108.6, 108.2, 108.0 (**C8, C9, C3'', C4''**), 58.4 (**C6**), 56.4 (**C3**), 55.9, 55.8, 55.7 (3xO**C**H_3), 55.6 (**C3**), 55.3, 55.2 (O**C**H_3), 52.8, 50.6 (**C11a**), 49.2 (**C6**), 35.1, 30.4 (**C**H_2-C3), 28.1, 27.3 (**C11**).

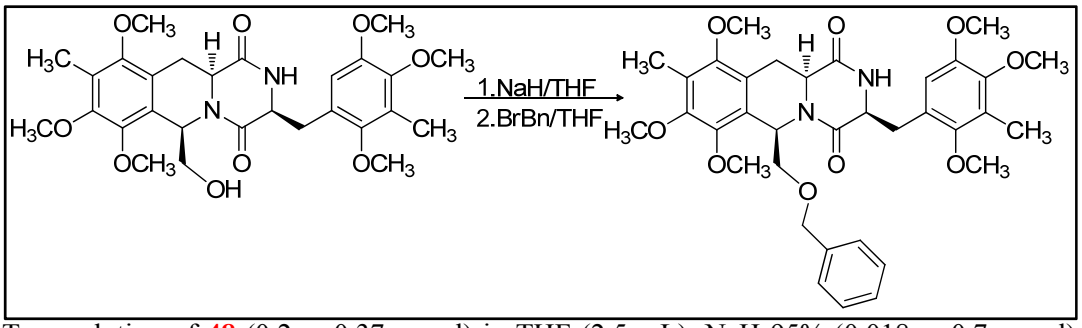
5.4.7. Synthesis of (±)-(3*S**,6*R**, *11aS**)-6-(hydroxymethyl)-7,8,10-trimethoxy-9-methyl-3-(2,4,5-trimethoxy-3-methylbenzyl)-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 48.



To compound **43a** (0.1 g, 0.16 mmol) in CCl_4 (1.0 mL) CH_3CN (1.0 mL) and H_2O (1.5 mL), $RuCl_3.nH_2O$ (0.80 mg, 0.0038 mmol) and $NaIO_4$ (0.078 g, 0.36 mmol) were added. The reaction mixture was stirred during 30 min at room temperature followed by the addition of $NaIO_4$ (0.078 g, 0.36 mmol) at room temperature and the reaction was stirred for 12 h. The crude was filtered through celite to removed the $RuCl_3$ and DCM (3x 30 mL) was added to extract compound **47**. The mother liquor was extracted with DCM (2x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to obtain **47** as an unstable brown oil**.** To the mixture $NaCNBH_3$ (0.033 g, 0.53 mmol) and THF (1.0 mL) were added and the reation was stirred for 12 h at room temperature. The crude was extracted with DCM (3x 10 mL), concentrated *in vacuo* and purified by flash column chromatography using a

mixture of 9:1 ethyl acetate:methanol as eluent to obtain compound **48** (0.033 g, 0.060 mmol) as a pale yellow solid in 60% yield **Mp** 118–120 ºC; **IR (NaCl)** ν_{max} 3364, 2934, 2361, 1668 cm^{-1}; **Analysis**: Calcd.for $C_{28}H_{36}N_2O_9$: C, 61.75; H, 6.66; N, 5.14 Found: C, 61.69; H, 6.61; N, 5.17.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.87 (b.s, 1H, N**H**), 6.42 (s, 1H, C$\mathbf{H}_{Ar}$), 5.95 (dd, *J* = 8.9, 3.7 Hz, 1H, **H6**), 4.48-4.40 (m, 1H, **H3**), 4.34 (dd, *J* = 12.0, 4.5 Hz, 1H, **H11a**), 3.98 (dd, *J* = 11.6, 3.8 Hz, 1H, **H1'**), 3.88 (s, 3H, OC$\mathbf{H}_3$), 3.76 (s, 3H, OC$\mathbf{H}_3$), 3.66 (s, 3H, OC$\mathbf{H}_3$), 3.61 (s, 3H, OC$\mathbf{H}_3$), 3.55 (s, 3H, OC$\mathbf{H}_3$), 3.40 (s, 3H, OC$\mathbf{H}_3$), 3.29 – 2.98 (m, 5H, **H1'**, **H11**, C$\mathbf{H}_2$-C3, -O**H**), 2.13 (s, 3H, C$\mathbf{H}_3$), 2.11 (s, 3H, C$\mathbf{H}_3$), 1.71 (dd, *J* = 16.2, 12.5 Hz, 1H, **H11**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 167.4 (**C4**), 165.4 (**C1**), 152.4, 151.5, 150.2, 149.3, 147.3, 146.0 (6x**C**-OCH_3), 125.9, 125.1 (**C-Ar, C10a**), 123.2, 123.1 (**C**-CH_3, **C9**) , 121.9 (**C6a**), 111.4 ($\mathbf{C}H_{Ar}$), 63.0 (**C1'**), 60.7, 60.6, 60.2 (3xOCH_3), 60.1 (2xOCH_3), 56.4 (**C3**), 55.4 (OCH_3), 51.3, 51.2 (**C6, C11a**), 34.9 (CH_2-C3), 27.9 (**C11**), 9.8, 9.4 (2xCH_3).

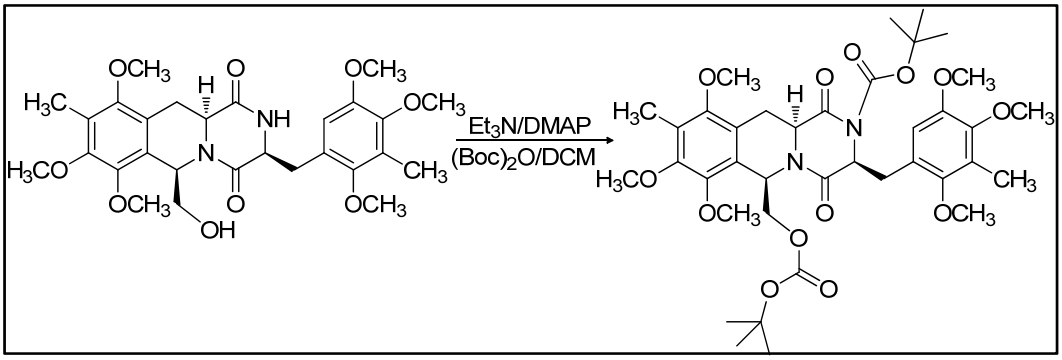
5.4.8. Synthesis of (±)-(3*S**,6*R**, *11aS**)-6-benzoxymethyl-7,8,10-trimethoxy-9-methyl-3-(2,4,5-trimethoxy-3-methylbenzyl)-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione 49.



To a solution of **48** (0.2 g, 0.37 mmol) in THF (2.5 mL), NaH 95% (0.018 g, 0.7 mmol) was added and stirred at room temperature for 2 h. Then, BrBn (0.083 mL, 0.7 mmol) was added at room temperature and stirred for 6.5 h more. The crude was extracted with DCM (3x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under pressure. The oil was purified by flash column chromatography using ethyl acetate as eluent to obtain **49¡** (0.134 g, 0.21 mmol) as a pale yellow solid in 60 % yield. **Mp** 98–100 ºC; **IR (NaCl)** ν_{max} 3428, 2938, 1656 cm^{-1}; **Analysis**: Calcd.for $C_{35}H_{42}N_2$: C, 66.23; H, 6.67; N, 4.41. Found: C, 66.33; H, 6.59; N, 4.40.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.37-7.25 (m, 6H, **H2'' - H6''**, N**H**), 6.33 (s, 1H, C$\mathbf{H}_{Ar}$), 5.84 (dd, *J* = 8.4, 3.7 Hz, 1H, **H6**), 5.65 (d, *J* = 14.9 Hz, 1H, O$\mathbf{CH}_2$), 4.39 (dd, *J* = 12.6, 4.4 Hz, 1H, **H11a**), 4.28 (t, *J* = 4.0 Hz, 1H, **H3**), 4.03 (d, *J*=14.9Hz, 1H, O$\mathbf{CH}_2$), 3.99 (dd, J=8.9, 4.0 Hz, 1H, O$\mathbf{CH}_2$-C6), 3.87 (s, 3H, OC$\mathbf{H}_3$), 3.76 (s, 3H, OC$\mathbf{H}_3$), 3.75 – 3.68 (m, 1H, O$\mathbf{CH}_2$-C6), 3.64 (s, 3H, OC$\mathbf{H}_3$), 3.60 (s, 3H, OC$\mathbf{H}_3$),

3.51 (s, 3H, OC**H$_3$**), 3.35 (s, 3H, OC**H$_3$**),3.28 (dd, *J* = 14.0, 4.5 Hz 1H, C**H$_2$**-C3), 3.17 – 3.04 (m, 2H, **CH$_2$**-C3, **H11**), 2.12 (s, 3H, C**H$_3$**), 2.04 (s, 3H, C**H$_3$**), 1.19 (dd, *J* = 16.5, 12.5 Hz, 1H, **H11**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 165.4 , 165.2 (**C1, C4**), 152.3, 152.0, 150.1, 149.1, 147.5, 145.9 (6x**C**-OCH_3), 135.5 (**C1''**), 129.1, 128.9 (**C2'', C3'', C5'', C6''**), 128.2 (**C4''**), 125.8, 125.2(**C$_{Ar}$**, **C10a**), 122.6, 122.5, 122.4 (**C6a**, **C9**, **C$_{Ar}$**-Me), 111.6 (**C**H_{Ar}), 68.1, 64.2 (O**C**H_2-C6), 60.6, 60.4, 60.1, 60.1, 60.0 (5xO**C**H_3), 59.0 (**C3**), 55.4 (O**C**H_3), 51.9 (**C11a**), 51.4 (**C6**), 46.8 (O**C**H_2), 31.5 (**C**H_2-C3), 28.0, 25.7 (**C11**), 9.8, 9.4 (2x**C**H_3).

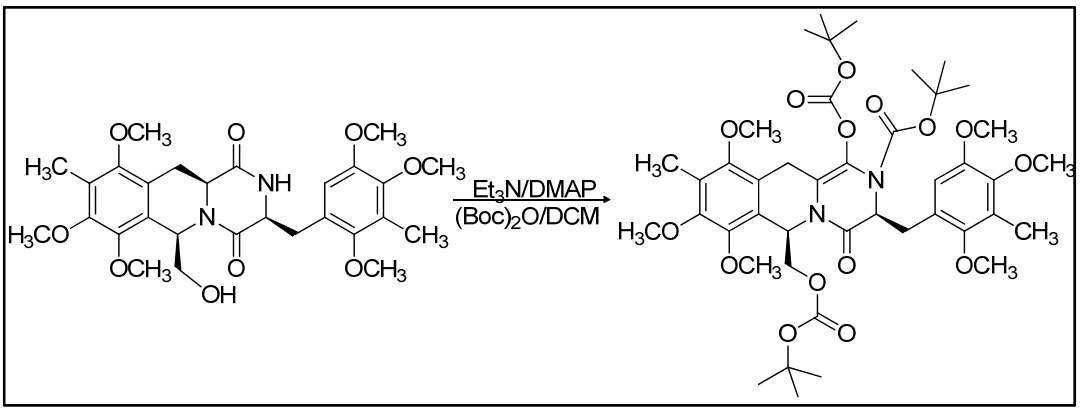
5.4.9. Synthesis of (±)-(3S*,6*R**, *11aS**)-*tert*-butyl 6-*tert*-butoxycarbonyloxymethyl-9-methyl-7,8,10-trimethoxy-3-(2,4,5-trimethoxy-3-methylbenzyl)-1,4-dioxo-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-2-carboxylate 50.



To a solution of **48** (0.35 g, 0.62 mmol), DMAP (0.076, 0.62 mmol) and $(Boc)_2O$ (1.36 g, 6.25 mmol) in DCM (0.8 mL) Et_3N (0.087 mL, 0.62 mmol) was added at 40 ºC and the reaction was stirred for 12 h. The crude was extracted with DCM (3x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The oil was purified by flash column chromatography using a mixture of 8:2 petroleum ether:diethyl ether as eluent to obtain **50** (0.028 g, 0.062 mmol) as a brown solid in 86% yield. **Mp** 100–102 ºC; **IR (NaCl) ν_{max}** 3350, 2931, 2332, 1645 cm^{-1}; **Analysis**: Calcd.for $C_{38}H_{52}N_2O_{13}$: C, 61.28; H, 7.04; N, 3.76. Found: C, 61.20; H, 6.98; N, 3.66.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.34 (s, 1H, C**H$_{Ar}$**), 6.08 (t, *J* = 6.1 Hz, 1H, **H6**), 5.05 (t, *J* = 4.6 Hz, 1H, **H3**), 4.49 (dd, *J* = 12.5, 4.8 Hz, 1H, **H11a**), 4.32 (d, *J* = 6.2 Hz, 2H, **H1'**), 3.89 (s, 3H, OC**H$_3$**), 3.76 (s, 3H, OC**H$_3$**), 3.65 (s, 3H, OC**H$_3$**), 3.53-3.55 (m, 7H,

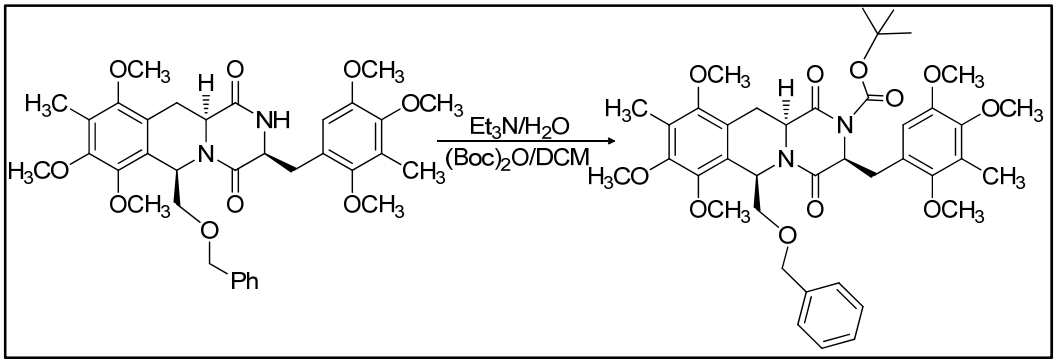
2xOC**H**$_3$, C**H**$_2$-C3), 3.33 (s, 3H, OC**H**$_3$), 3.12 (m, 1H, **H11**), 3.05 (t, *J* = 4.6 Hz, 1H, C**H**$_2$-C3), 2.13 (s, 3H, C**H**$_3$), 2.07 (s, 3H, C**H**$_3$), 1.55 (s, 9H, C-(C**H**$_3$)$_3$), 1.42 (s, 9H, C-(C**H**$_3$)$_3$), 1.22- 1.15(m, 1H, **H11**).; ^{13}**C NMR** (63 MHz, $CDCl_3$) δ 166.0, 164.3 (**C1, C4**), 153.4, 152.4, 151.9, 150.7, 150.2, 149.1, 147.5, 146.1 (6xO**C**H$_3$, 2x **C**O-C-(CH$_3$)$_3$) 126.0, 125.5, 122.8, 122.4, 121.6 (**C**$_{Ar}$, **C**$_{Ar}$-CH$_3$, **C6a, C9, C10a**), 112.0 (**C**H$_{Ar}$), 84.0, 82.4 (2x**C**-(CH$_3$)$_3$), 65.3 (**C1'**), 60.6, 60.4, 60.2, 60.1, 60.0 (5xO**C**H$_3$), 59.4 (**C1'**), 55.4 (O**C**H$_3$), 52.9(**C11a**), 48.5 (**C6**), 33.7 (**C**H$_2$-C3), 28.0, 27.7 (C-(**C**H$_3$)$_3$), 27.0 (**C11**), 9.8, 9.4 (2x**C**H$_3$).

5.4.10. Synthesis of (±)-(3*S**,6*R**)-*tert*-butyl 1-*tert*-butoxycarbonyloxy-6-*tert*-butoxycarbonyloxymethyl-7,8,10-trimethoxy-9-methyl-4-oxo-3-(2,4,5-trimethoxy-3-methylbenzyl)-2,3,6,11-tetrahydropyrazino[1,2-*b*]isoquinoline-2-carboxylate 51.


OCH3
O
OCH3
H3C
NH
OCH3
N
Et3N/DMAP
(Boc)2O/DCM
H3CO
CH3
OCH3
O
OCH3
OH
O
O
O

867.3889; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.55 (s, 1H, C**H**$_{Ar}$), 6.23 (t, *J* = 5.8 Hz, 1H, **H6**), 4.21 (d, *J* = 5.7 Hz, 2H, **H1'**), 3.92 (s, 3H, OC**H**$_3$), 3.82 (s, 3H, OC**H**$_3$), 3.80 (s, 3H, OC**H**$_3$), 3.74 (s, 3H, OC**H**$_3$), 3.68 (s, 3H, OC**H**$_3$), 3.56 (s, 3H, OC**H**$_3$), 3.61-3.50 (m, 3H, 2x**H11, H3**), 3.01 (dd, *J* = 13.4, 4.8 Hz, 1H, C**H**$_2$-C3), 2.51 (dd, *J* = 13.2, 11.0 Hz, 1H, C**H**$_2$-C3), 2.20 (s, 3H, C**H**$_3$), 2.11 (s, 2H, C**H**$_3$), 1.56 (s, 9H, C-(C**H**$_3$)$_3$), 1.39 (s, 9H, C-(C**H**$_3$)$_3$), 1.25 (bs, 9H, C-(C**H**$_3$)$_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 165.7 (**C4**), 153.2, 151.2, 150.9, 150.2, 149.8, 149.7, 148.8, 146.6, 146.2 (6xOCH$_3$, 3x**C**O-C(CH$_3$)$_3$), 125.7, 125.6, 125.1, 125.0, 124.3, 120.5 (**C**$_{Ar}$, **C**-CH$_3$, **C6a, C9, C10a, C11a**) , 112.3 (**C**H-Ar), 83.6, 82.1, 81.9, 81.8 (**C1**, 3x**C**-(CH$_3$)$_3$), 67.1 (**C1'**), 60.8, 60.7, 60.4, 60.2, 60.2 55.9, 46.6 (**C6**), 30.4 (**C**H$_2$-C3), 28.0, 27.8, 27.8 (C-(**C**H$_3$)$_3$), 20.8 (**C11**), 9.7, 9.5 (2x**C**H$_3$).

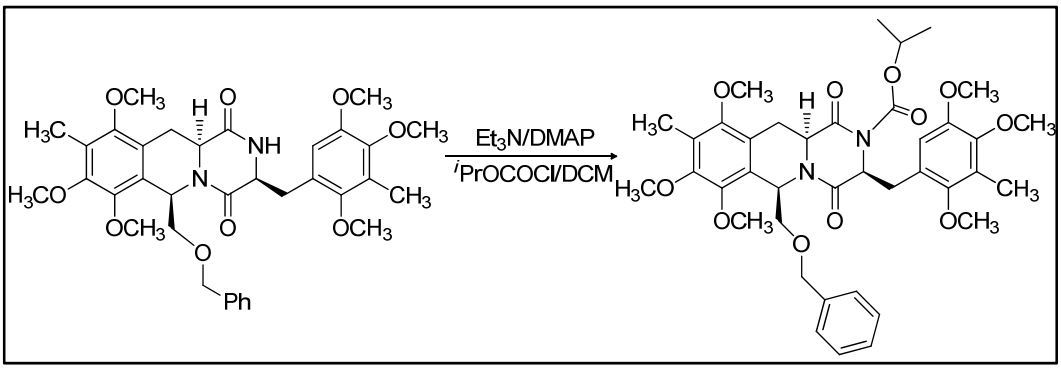
5.4.11. Synthesis of (±)-(3*S**,6*R**, *11aS**)-*tert*-butyl 6-benzyloxymethyl-7,8,10-trimethoxy-9-methyl-1,4-dioxo-3-(2,4,5-trimethoxy-3-methylbenzyl)-3,4,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-2-carboxylate 52.



To a solution of **49** (0.22 g, 0.36 mmol) and $(Boc)_2O$ (0.33 g, 1.44 mmol) in anhydrous DCM (1.0 mL) anhydrous Et_3N (0.50 mL, 3.60 mmol) and H_2O (0.25 μL) were added at room temperature for 12 h. The crude was extracted with DCM (3x 20 mL), was dried over anhydrous Na_2SO_4, was filtered and was concentrated under pressure. The oil was purified by flash column chromatography using a mixture of 5:5 diethyl ether:ethyl acetate as eluent to obtain **52** (0.21 g, 0.28 mmol) as a pale yellow solid in 78% yield. **Mp** 100–102 ºC; **IR (NaCl) ν_{max}** 2939, 1740, 1660 cm^{-1}; **Analysis**: Calcd.for $C_{40}H_{50}N_2O_{11}$: C, 65.38; H, 6.86; N, 3.81. Found: C, 65.22; H, 6.86; N, 3.85; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.48 – 7.29 (m, 5H, **H2'' - H6''**), 6.34 (s, 1H, C**H**-Ar), 6.00 (dd, *J* = 8.2, 2.9 Hz, 1H, **H6**), 5.69 (d, *J* = 15.0 Hz, 1H, OC**H**$_2$), 4.51 – 4.31 (m, 2H, OC**H**$_2$-C6, **H11a**), 4.26-4.19 (m, 2H, OC**H**$_2$-C6, **H3**), 4.01 (d, *J* = 15.0 Hz, 1H, OC**H**$_2$), 3.89 (s, 3H, OC**H**$_3$), 3.76 (s, 3H, OC**H**$_3$), 3.70 (s, 3H, OC**H**$_3$), 3.64 (s, 3H, OC**H**$_3$), 3.60 (s, 3H, OC**H**$_3$), 3.51 (s, 3H, OC**H**$_3$), 3.39 –

3.26 (m, 1H, C**H**$_2$-C3), 3.15-3.13 (m, 1H, C**H**$_2$-C3), 3.10-3.06 (m, 1H, **H11**), 2.12 (s, 3H, C**H**$_3$), 2.07 (s, 3H, C**H**$_3$), 1.30 (s, 9H, C-(C**H**$_3$)$_3$), 1.20 – 1.13 (m, 1H, **H11**).; ^{13}**C NMR** (63 MHz, $CDCl_3$) δ 165.4, 164.1 (**C1, C4**), 153.5, 152.2, 151.9, 150.0, 149.1, 147.4, 146.0 (**C**-OCH_3, **C**O-O^{t}Bu), 135.7 (**C1''**), 129.0, 128.9 (**C2'', C3'', C5'', C6''**), 128.0 (**C4''**), 125.8, 125.4, 122.8, 122.7, 121.7 (**C**-Me, **C**-Ar, **C6a, C9, C10a**), 111.6 (**C**H$_{Ar}$), 82.1 (**C**-$(CH_3)_3$), 65.9 (O**C**H$_2$-C6), 60.6 (**C3**), 60.4, 60.1, 60.0, 60.0, 58.9, 55.3 (6xO**C**H$_3$), 51.8 (**C11a**), 48.9 (**C6**), 46.6 (O**C**H$_2$), 31.3 (**C**H$_2$-C3), 27.9 (**C11**), 27.7 (C-(**C**H$_3$)$_3$), 9.8, 9.4 (**C**$_{Ar}$- **C**H$_3$, C9- **C**H$_3$).

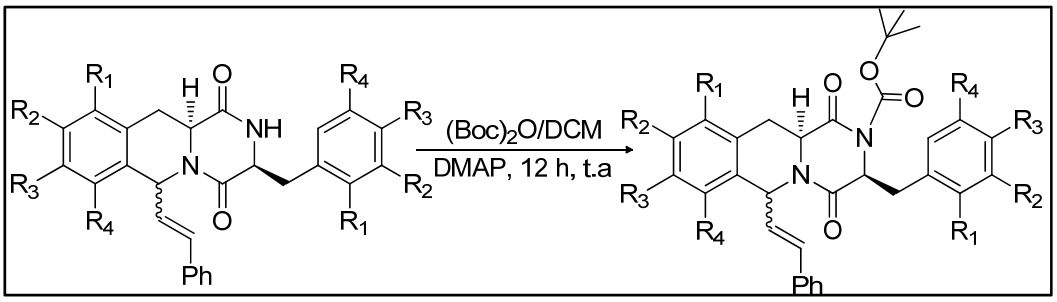
5.4.12. Synthesis of (±)-(3*S**,6*R**, *11aS**)-isopropyl 6-benzyloxymethyl-7,8,10-trimethoxy-9-methyl-1,4-dioxo-3-(2,4,5-trimethoxy-3-methylbenzyl)-3,4,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-2-carboxylate 53.



To a solution of **49** (0.15 g, 0.24 mmol) and DMAP (0.12, 0.97 mmol) in DCM (0.8 mL), isopropyl chloroformate 1.0 M (0.73 mL , 0.73 mmol) and Et_3N (0.14 mL, 0.97 mmol) were added at room temperature and the reaction was stirred for 48 h. The crude was extracted with DCM (3x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The oil was purified by flash column chromatography using a mixture of 5:5 petroleum ether: diethyl ether as eluent to obtain **53** (0.13 g, 0.18 mmol) as a clear yellow oil in 80 % yield. **IR (NaCl) ν_{max}** 2937, 1740, 1663 cm^{-1}; **Analysis**: Calcd.for $C_{39}H_{48}N_2O_{11}$: C, 64.99; H, 6.71; N, 3.89. Found: C, 65.09; H, 6.75; N, 3.81; ^{1}**H NMR** (250 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H, C_6**H**$_5$), 6.35 (s, 1H, C**H**$_{Ar}$), 6.02 (dd, *J* = 8.2, 3.2 Hz, 1H, **H6**), 5.69 (d, *J* = 15.1 Hz, 1H, OC**H**$_2$), 4.75 – 4.56 (m, 1H, C**H**-$(CH_3)_2$), 4.50 – 4.37 (m, 2H, OC**H**$_2$-C6, **H11a**), 4.32 (dd, *J* = 11.7, 3.4 Hz, 1H, OC**H**$_2$-C6), 4.20 (t, *J* = 4.2 Hz, 1H, **H3**), 3.99 (d, *J* = 15.1 Hz, 1H, OC**H**$_2$), 3.89 (s, 3H, OC**H**$_3$), 3.76 (s, 3H, OC**H**$_3$), 3.64 (s, 3H, OC**H**$_3$), 3.60 (s, 3H, OC**H**$_3$), 3.51 (s, 3H, OC**H**$_3$), 3.30 (s, 3H, OC**H**$_3$), 3.38 – 3.25 (m, 1H, C**H**$_2$-C3), 3.18 – 3.02 (m, 2H, C**H**$_2$-C3, **H11**), 2.12 (s, 3H, C**H**$_3$), 2.08

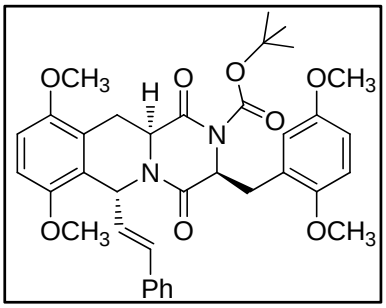
(s, 3H, C**H**$_3$), 1.20 (d, *J* = 6.1 Hz, 3H, CH-(C**H**$_3$)$_2$), 1.13 (m, 1H, **H11**), 1.07 (d, *J* = 6.3 Hz, 3H, CH-(C**H**$_3$)$_2$); ^{13}**C NMR** (63 MHz, $CDCl_3$) δ 165.3 (**C4**), 164.2 (**C1**), 154.7 (CO-O^{i}Pro), 152.3 (**C**-OCH$_3$), 151.9 (**C8**), 150.0 (**C**-OCH$_3$), 149.1 (**C10**), 147.4, 146.0(2x**C**-OCH$_3$), 135.6 (**C1''**), 128.9, 128.7 **(C2'', C3'',C5'',C6'')**, 128.2, 128.0 (**C4''**), 125.8 (**C**-CH$_3$), 125.4 (**C9**), 122.8, 122.7, 121.5 (**C$_{Ar}$, C6a, C10a**), 111.6 (**CH$_{Ar}$**), 72.1 (**C**H-(CH$_3$)$_2$), 66.2 (O**C**H$_2$-C6), 60.6 , 60.4, 60.1, 60.0, 59.9 (5xO**CH$_3$**), 58.8(**C3**) , 55.3 (C10-O**C**H$_3$), 51.8 (**C11a**) , 48.7 (**C6**), 46.6 (O**CH$_2$**), 31.3 (C3-**C**H$_2$), 27.8 (**C11**), 21.8 (CH-(**C**H$_3$)$_2$), 21.8 (CH-(**C**H$_3$)$_2$), 9.8, 9.4 (2x**C**H$_3$).

5.4.13. General procedure to obtain (±)-(3*S**, *11aS**,*E*)-2-*tert*-butyl 3-benzyl-1,4-dioxo-6-styryl-3,4,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-2-carboxylates 54 – 55.



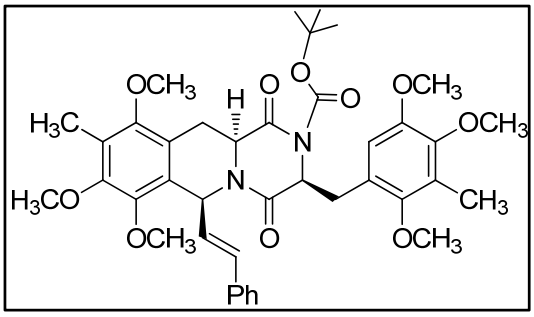
To a solution of **42b** or **43a** (1.0 eq), $(Boc)_2O$ (4.0 eq) and DMAP (1.1 eq) in dry DCM (20–100 eq) was stirred for 12 h at room temperature. The crude was extracted with DCM (3x 20 mL), was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The oil was purified by flash column chromatography using a mixture 2:8 petroleum ether: diethyl ether as eluent to obtain **54** or **55**.

5.4.13.1. Synthesis of (±)-(3S*,6*R**, *11aS**,*E*)-2-*tert*-butyl 3-(2,5-dimethoxybenzyl)-7,10-dimethoxy-1,4-dioxo-6-styryl-3,4,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-2-carboxylate 54.



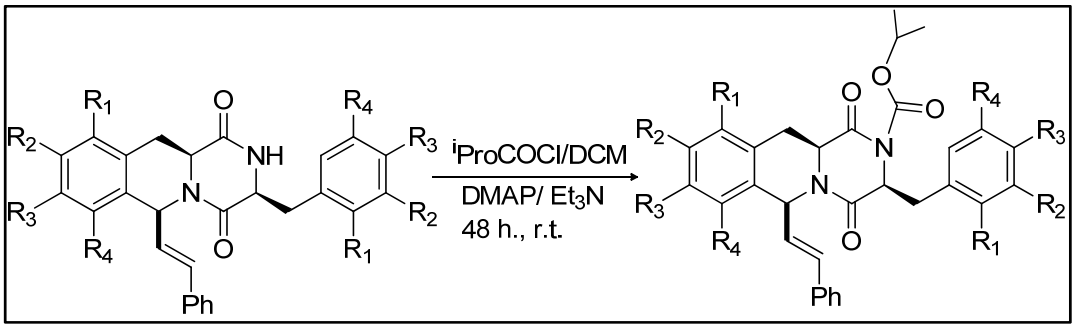
Obtained according to the general procedure **4.3.13** using compound **42b** (0.57 g, 0.90 mmol) as starting material, DMAP (0.12 g, 0.99 mmol), $(Boc)_2O$ (0.79 g, 3.62 mmol) and dry DCM (2.0 mL) as solvent. Purification by flash column chromatography on silica gel using a mixture of 2:8 petroleum ether: diethyl ether as eluent afforded product **54** (0.45 g, 0.72 mmol) as a brown solid in 80% yield as a mixture of rotamers in $CDCl_3$, 25ºC. **Mp** 168–169 ºC; **IR (NaCl)** ν_{max} 3200, 2930, 1693, 1625 cm^{-1}; **Analysis**: Calcd.for $C_{36}H_{40}N_2O_8$: C, 68.77; H, 6.41; N, 4.46. Found: C, 68.56; H, 6.28; N, 4.30; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 3H, C**H$_{Ar}$**), 6.75 – 6.64 (m, 6H, C**H$_{Ar}$**), 6.59 (s, 1H, **H6**), 6.39 (d, *J* = 2.8 Hz, 1H, **H6'''**), 6.22 (dd, *J* = 16.1, 4.6 Hz, 1H, **H1'**), 6.07 (d, *J* = 15.9 Hz, 1H, **H2'**), 5.11 (t, *J* = 4.4 Hz, 1H, **H3**), 4.32 (dd, *J* = 12.3, 5.8 Hz, 1H, **H11a**), 3.68 (m, 9H, 3xO**C**H$_3$), 3.34 (dd, *J* = 13.6, 4.5 Hz, 1H, C**H$_2$**-C3), 3.09 (s, 1.5H, OC**H$_3$**), 3.06 (s, 1.5H, OC**H$_3$**), 3.00 - 2.92 (m, 1H, C**H$_2$**-C3), 2.86 (dd, *J* = 17.8, 5.5 Hz, 1H, **H11**), 1.56 (s, 4H, OC(C**H$_3$**)$_3$), 1.28 (s, 2.4H, OC(C**H$_3$**)$_3$), 1.25 (s, 2.6H, OC(C**H$_3$**)$_3$) 0.87 (dd, *J* = 17.6, 12.5 Hz, 1H, **H11**); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.5, 166.9, 163.6, 161.1 (**C1, C4**), 153.5, 153.2, 152.3, 152.3, 152.2, 151.1, 150.0, 149.8, 149.7, 149.5 (4x**C**-OCH$_3$, **C**OOC(CH$_3$)$_3$), 136.3* (**C1''**), 133.1 (**C2'**), 129.9, 128.5, 127.9, 127.3, 126.6 (**C2'' - C6''**), 126.4 (**C1'**), 125.2, 124.5, 123.7, 123.2, 122.7* (**C6a, C10a**), 117.7, 117.0, 115.9, 115.2 (**C6'''**), 113.2, 111.7, 111.4, 111.1, 108.7, 108.5, 107.9 (**C8, C9, C3''', C4'''**), 83.9, 83.8, 83.8 (O**C**(CH$_3$)$_3$), 60.5, 60.2, 59.9 (**C3**), 56.1, 55.8, 55.7, 55.6, 55.4, 55.3, 54.9, 54.7 (4xO**C**H$_3$), 52.0 (**C11a**), 48.9 (**C6**), 35.0, 33.3 (**C**H$_2$-C3), 28.1, 28.0, 27.8, 27.8, 27.8, 27.6 (OC(**C**H$_3$)$_3$), 27.0 (**C11**).

5.4.13.2. Sythesis of (±)-(3*S,6*R**, *11aS**,*E*)-*tert*-butyl 7,8,10-trimethoxy-9-methyl-1,4-dioxo-6-styryl-3-(2,4,5-trimethoxy-3-methylbenzyl)-3,4,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-2-carboxylate 55.**



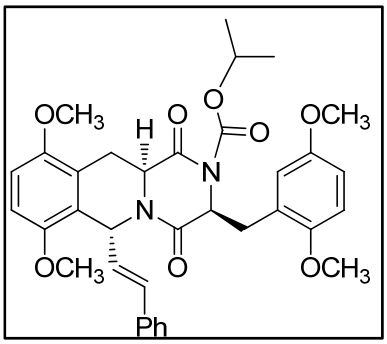
Obtained according to the general procedure **4.3.13** using compound **43a** (0.50 g, 0.80 mmol) as starting material, DMAP (0.109 g, 0.89 mmol), $(Boc)_2O$ (0.70 g, 3.20 mmol) and dry DCM (5.0 mL) as solvent. Purification by flash column chromatography on silica gel using a mixture of 2:8 petroleum ether:diethyl ether as eluent afforded product **55** (0.47 g, 0.65 mmol) as a brown oil in 81% yield. **IR (NaCl) ν_{max}** 2938, 2836, 2361 cm^{-1}; **Analysis**: Calcd.for $C_{40}H_{48}N_2O_{10}$: C, 67.02; H, 6.75; N, 3.91. Found: C, 66.89; H, 6.70; N, 3.82.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 5H, **H2'' - H6''**), 6.56 (d, *J* = 5.1 Hz, 1H, **H6**), 6.36 (s, 1H, **CH**$_{Ar}$), 6.29 (dd, *J* = 15.9, 5.3 Hz, 1H, **H1'**), 6.14 (dd, *J* = 15.9 Hz, 1H, **H2'**), 5.08 (t, *J* = 4.7 Hz, 1H, **H3**), 4.29 (dd, *J* = 12.5, 4.8 Hz, 1H, **H11a**), 3.76 (s, 6H, 2xOC**H$_3$**), 3.66 (s, 3H, OC**H$_3$**), 3.56 (s, 3H, OC**H$_3$**), 3.55 (m, 3H, OC**H$_3$**), 3.50 (t, *J* = 4.6 Hz, 1H, **CH$_2$**-C3), 3.36 (s, 3H, OC**H$_3$**), 3.14 – 3.12 (m, 1H, **H11**), 3.07 (t, *J* = 4.6 Hz, 1H, C**H$_2$**-C3)2.17 (s, 3H, **CH$_3$**), 2.09 (s, 3H, C**H$_3$**), 1.53 (s, 9H, C- (C**H$_3$)$_3$**), 1.34 – 1.27 (m, 1H, **H11**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 166.3 (**C1**), 163.4 (**C4**), 152.2* (**C7**), 151.9 (**C**-OCH_3), 150.6 (**C**O-O^{t}Bu), 150.2* (**C8**), 149.0, 147.4 (2x**C**-OCH_3), 146.0* (**C10**), 136.0 (**C1''**), 133.6 (**C2'**), 128.6 (**C3'', C5''**), 128.1 (**C4''**), 127.0 (**C1'**), 126.6 (**C2'', C6''**), 125.9, 125.0, 124.4 (**C**-Ar**, C6a, C10a**), 122.8 (**C**-Me), 121.8 (**C9**), 111.9 (**CH**$_{Ar}$), 84.1 (**C**-$(CH_3)_3$), 60.4, 60.3, 60.1, 60.0, 59.9(5xO**C**H_3), 59.7 (**C3**), 55.3 (O**C**H_3), 52.4 (**C11a**), 49.4 (**C6**), 33.8 (**C**H_2-C3), 28.0 (C- **(C**$H_3)_3$), 27.2(**C11**), 9.8, 9.4 (2x**C**H_3).

5.4.14. General procedure to obtain (±)-(3*R**, *11aS*, 1'*E*)-isopropyl 3-benzyl-1,4-dioxo-6-styryl-3,4,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-2-carboxylate 56–57.



To a solution of **42b** or **43a** (1.0 eq), $(Boc)_2O$ (4.0 eq) and DMAP (4.0 eq) in dry DCM (1.5 mL), Et_3N (4.0 eq) and isopropyl chloroformate (3.0 eq) were added and was stirred for 48 h at room temperature. The crude was extracted with DCM (3x 20 mL), was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The oil was purified by flash column chromatography using a mixture of 2:8 petroleum ether: diethyl ether as eluent to obtain compounds **56** or **57**.

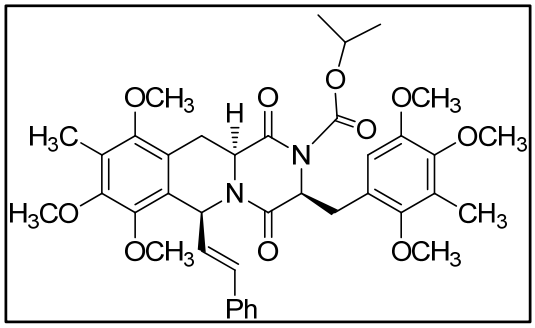
5.4.14.1. Synthesis of (±)-(3*R**, 6*R**, *11aS**,1'*E*)-isopropyl 3-(2,5-dimethoxybenzyl)-7,10-dimethoxy-1,4-dioxo-6-styryl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-2-carboxylate 56.



Obtained according to the general procedure **4.3.14** using compound **42b** (0.30 g, 0.49 mmol) as starting material, DMAP (0.24 g, 1.96 mmol), 1.0M ^{i}PrOCOCl (1.47 mL, 1.47 mmol) and dry DCM (1.5 mL) as solvent. Purification by flash column chromatography on silica gel using a mixture of 2:8 petroleum ether:diethyl ether as eluent afforded product **56** (0.24 g, 0.39 mmol) as a brown solid in 80% yield as a mixture of rotamers in $CDCl_3$, 25 ºC. **Mp** 88–89 ºC; **IR (NaCl)** ν_{max} 2930, 2360, 1776, 1590 cm^{-1}; **Analysis**: Calcd.for $C_{35}H_{38}N_2O_8$: C, 68.39; H, 6.23; N,

4.56 Found: C, 68.46; H, 6.35; N, 4.70.; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 3H, C**H$_{Ar}$**), 6.80 – 6.62 (m, 6H, C**H$_{Ar}$**), 6.60 (dd, *J* = 4.6, 1.1 Hz, 1H, **H6**), 6.39 (d, *J* = 3.0 Hz, 1H, **H6''**), 6.22 (dd, *J* = 16.0, 4.7 Hz, 1H, **H1'**), 6.08 (dd, *J* = 16.0, 1.3 Hz, 1H, **H2'**), 5.19 – 5.14 (m, 2H, **H3**, OC**H**$(CH_3)_2$), 4.34 (dd, *J* = 12.3, 5.8 Hz, 1H, **H11a**), 3.81 – 3.59 (m, 9H, 3xOC**H$_3$**), 3.63 – 3.53 (m, 1H, C**H$_2$**-C3), 3.16 – 3.03 (m, 65H, C**H$_2$**-C3**,** OC**H$_3$**), 2.85 (dd, *J* = 18.0, 5.7 Hz, 1H, **H11**), 1.38 (m, 6H, OCH(C**H$_3$**)$_2$), 0.86 (dd, *J* = 18.1, 12.1 Hz, 1H, **H11**).; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.8, 163.4 (**C1, C4**), 153.5, 153.2 (**C**OOCH$(CH_3)_2$), 152.3, 152.2, 151.2, 151.1, 150.2, 150.0 (4x**C**-OCH$_3$), 136.2 (**C1''**), 133.1 (**C2'**), 128.5, 128.4* (**C2'', C6''**), 127.9 (**C4''**), 126.6, 126.6* (**C3'', C5''**), 126.3 (**C1'**), 123.6, 123.1, 122.7 (**C7a, C10a, C1'''**), 115.8, 115.3 (**C6'''**), 113.9, 111.7, 111.0, 110.2, 109.3, 108.5, 107.9 (**C8, C9, C3'', C4''**), ¡71.7, 71.6 (O**C**H$(CH_3)_2$), 60.2, 59.8 (**C11a**), 56.1, 55.8, 55.7, 55.6, 55.4, 54.9 (4xO**C**H$_3$), 51.9, 51.1 (**C3**), 48.9 (**C6**), 33.2 (**C11**), 27.0 (**C**H$_2$-C3), 21.9, 21.8 (OCH(**C**H$_3$)$_2$).

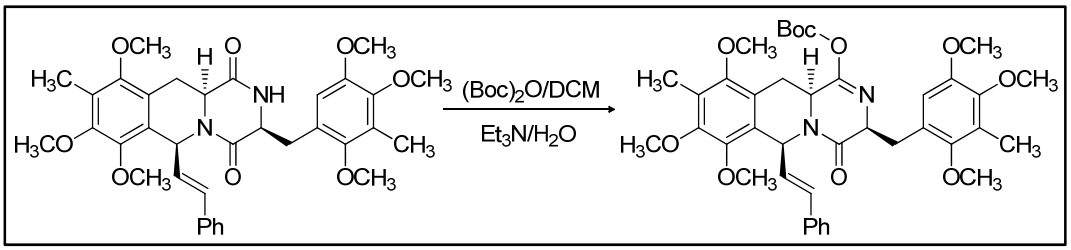
5.4.14.2. Synthesis of (±)-(3*S**,6*S**, *11aS**,1'*E*)-isopropyl 7,8,10-trimethoxy-9-methyl-1,4-dioxo-6-styryl-3-(2,4,5-trimethoxy-3-methylbenzyl)-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-2-carboxylate 57.



Obtained according to the general procedure **4.3.14** using compound **43a** (0.30 g, 0.49 mmol) as starting material, DMAP (0.24 g, 1.96 mmol), 1.0 M ^{i}PrOCOCl (1.47 mL, 1.47 mmol) and dry DCM (1.5 mL) as solvent. Purification by flash column chromatography on silica gel using a mixture of 2:8 petroleum ether: diethyl ether as eluent afforded product **57** (0.28 g, 0.39 mmol) as a brown solid in 80% yield. **Mp** 93–95 ºC; **IR (NaCl) ν_{max}** 2938, 2835, 2361 cm^{-1}; **Analysis:** Calcd.for $C_{39}H_{46}N_2O_{10}$: C, 66.65; H, 6.60; N, 3.99. Found: C, 66.60; H, 6.61; N, 3.90; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.34 – 7.16 (m, 5H, **H2'' - H6''**), 6.56 (d, *J* = 5.2 Hz, 1H, **H6**), 6.35 (s, 1H, C**H$_{Ar}$**), 6.29 (dd, *J* = 15.9, 5.3 Hz, 1H, **H1'**), 6.14 (dd, *J* = 15.9, 0.8 Hz, 1H, **H2'**), 5.19 – 5.06 (m, 2H, **H3,** C**H**-$(CH_3)_2$), 4.30 (dd, *J* = 12.5, 4.8 Hz, 1H, **H11a**), 3.77 (s, 6H, 2xOC**H$_3$**), 3.66 (s, 3H, OC**H$_3$**), 3.60 – 3.49 (m, 1H, C**H$_2$**-C3),3,50 (s, 6H, 2xOC**H$_3$**), 3.32 (s, 3H, OC**H$_3$**), 3.20 – 3.00 (m, 2H, C**H$_2$**-C3, **C11**), 2.17 (s, 3H, C**H$_3$**-C9), 2.10 (s, 3H, C**H$_3$**-C3'''), 1.39 (d, *J* = 6.2 Hz, 3H, CH-**(CH_3)$_2$**), 1.34 (d, *J* = 6.3 Hz, 3H, CH-**(CH_3)$_2$**), 1.26 – 1.19 (m, 1H, **C11**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 166.0 (**C1**), 163.3 (**C4**), 152.3 (**C**-OCH$_3$), 151.9, 151.9* (**C**O-O^{i}Pr, **C10**), 150.3, 149.1* (**C7, C8**), 147.5 (**C**-OCH$_3$), 146.1* (**C**-OCH$_3$), 136.0 (**C1''**), 133.6 (**C2'**), 128.7** (**C2''**, **C6''**), 128.1 (**C4''**), 126.9 (**C1'**), 126.7** (**C5''**, **C3''**), 126.0 (**C**-Me), 125.0 (**C9**), 124.3 (**C6a**),

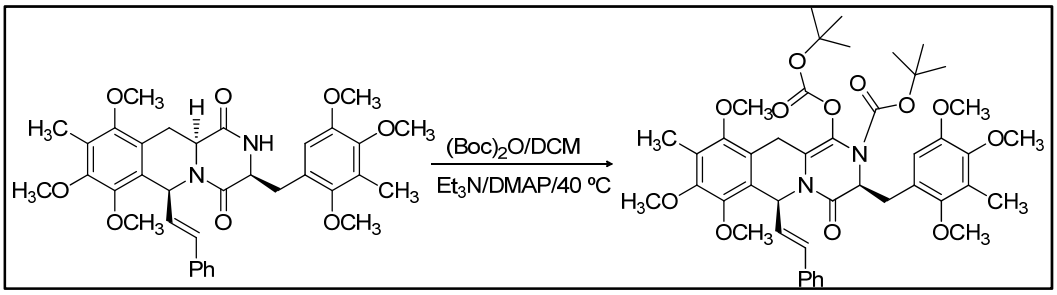
122.7 (**C**-Ar), 121.8 (**C10a**), 111.9 (**C**H_{Ar}), 72.1 (**C**H-(CH_3)$_2$) , 60.4, 60.3, 60.2, 60.1, 60.0 (5xO**C**H_3), 59.9 (**C3**), 55.3 (O**C**H_3), 52.4 (**C11a**), 49.4 (**C6**), 33.6 (CH_2-C3), 27.3 (**C11**), 21.9, 21.8 (2xCH-(**C**H_3)$_2$), 9.9 (**C**H_3-C3'''), 9.5 (**C**H_3-C9).

5.4.15. Synthesis of (±)-(3*R**, 6*S**, *11aS**, *E*)-*tert*-butyl (7,8,10-trimethoxy-9-methyl-4-oxo-6-styryl-3-(2,4,5-trimethoxy-3-methylbenzyl)-3,6,11,11a-tetrahydro-pyrazino[1,2-*b*]isoquinolin-1-yl)carbonate 58.



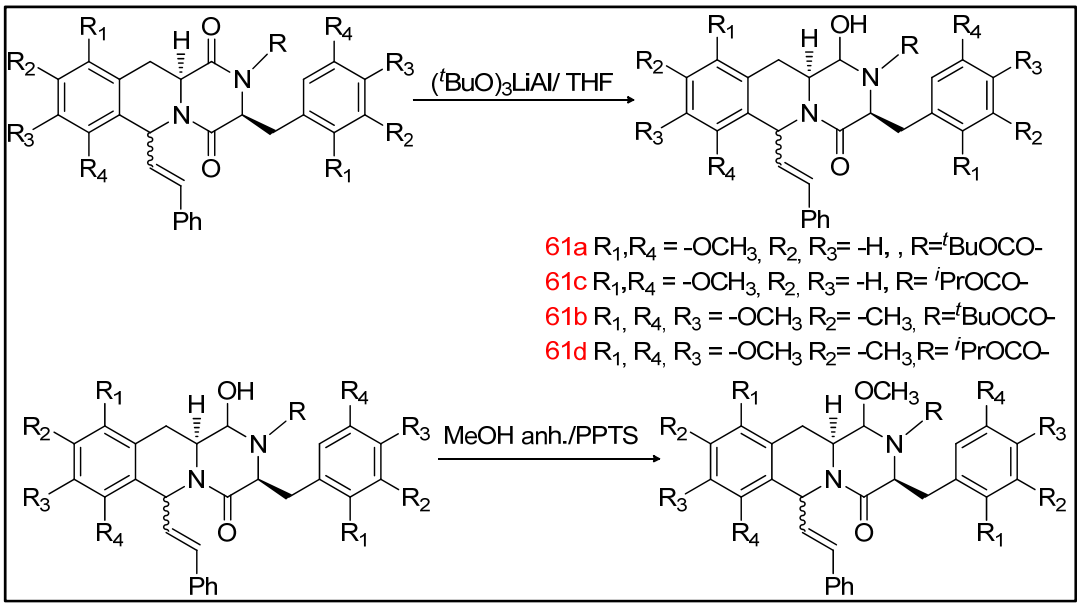
To a solution of **43a** (0.42 g, 0.68 mmol) and $(Boc)_2O$ (0.60 g, 1.31 mmol) in dry DCM (1.4 mL), dry Et_3N (0.093 mL, 0.68 mmol) and H_2O (3.5 µL) was added at room temperature and the reaction was stirred for 12 h. The crude was extracted with DCM (3x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The oil was purified by flash column chromatography using a mixture of 5:5 diethyl ether: ethyl acetate as eluent to obtain **58** (0.16 g, 0.22 mmol) as a pale yellow solid in 33% yield. **Mp** 103–105 ºC; **IR (NaCl) ν_{max}** 2938, 2361, 1686, 1596 cm^{-1}; **Analysis**: Calcd.for $C_{40}H_{48}N_2$: C, 67.02; H, 6.75; N, 3.91. Found: C, 66.90; H, 6.74; N, 3.91.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.34 – 7.08 (m, 5H, **H2'' - H6''**), 6.58(s, 1H, C**H**-Ar), 6.53 (s, 1H, **H6**), 6.37 (dd, *J* = 16.0, 5.3 Hz, 1H, **H1'**), 6.15 (dd, *J* = 15.8, 0.5 Hz, 1H, **H2'**), 4.53 (m, 1H, **H3**), 3.98 (m, 1H, **H11a**), 3.79 (s, 3H, O**C**H_3), 3.78 (s, 3H, O**C**H_3), 3.68 (s, 3H, O**C**H_3), 3.61 (s, 3H, O**C**H_3), 3.57 (s, 3H, O**C**H_3), 3.52 (s, 3H, O**C**H_3), 3.45 – 3.21 (m, 1H, CH_2-C3), 3.17 – 2.90 (m, 2H, CH_2-C3, **H11**), 2.20 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.79 (dd, *J* = 16.6, 12.4 Hz, 1H, **H11**), 1.40 (s, 9H, C-(C**H**$_3$)$_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 167.2 (**C4**), 157.0, 152.1, 151.5, 150.2, 148.6, 146.3, 146.3 (**C**-OCH_3, **C**O-O^{t}Bu), 136.5 (**C1''**), 132.6 (**C2'**), 128.6 (**C3'', C5''**), 127.8 (**C4''**), 127.7 (**C1'**), 126.6 (**C2'', C6''**), 125.8 (**C**-Me), 125.4** (**C10a**), 125.1* (**C6a**), 124.5** (**C-Ar**), 122.2* (**C9**), 111.4 (**CH**-Ar), 80.3 (**C**-(CH_3)$_3$), 60.4, 60.23, 60.2, 60.0, 60.0 (5xO**C**H_3), 59.9 (**C3**), 55.4 (O**C**H_3), 48.8, 48.7 (**C6, C11a**), 35.0 (CH_2-C3), 28.7 (**C11**), 28.2 (C-(**C**H_3)$_3$), 9.4, 9.3 (2x**C**H_3).

5.4.16. Synthesis of (±)-(3S*,6*S**,1'*E*)-*tert*-butyl 1-*tert*-butoxycarbonyloxy-7,8,10-trimethoxy-9-methyl-4-oxo-6-styryl-3-(2,4,5-trimethoxy-3-methylbenzyl)-2,3,6,11-tetrahydropyrazino[1,2-*b*]isoquinoline-2-carboxylate 59.



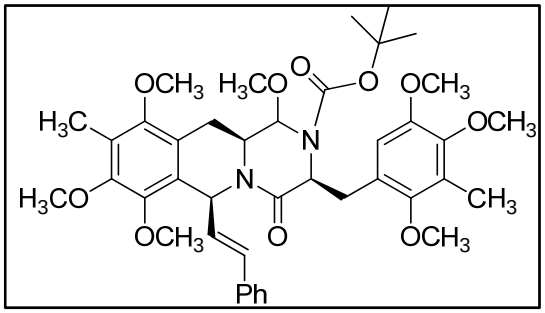
To a solution of **43a** (0.50 g, 0.79 mmol), DMAP (0.097 g, 0.79 mmol), $(Boc)_2O$ (0.69 g, 3.1 mmol) in anhydrous DCM (1.4 mL)and anhydrous Et_3N (1.1 mL, 7.9 mmol) was added at 40 ºC and the reaction was stirred for 12 h. The crude was extracted with DCM (3x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The oil was purified by flash column chromatography using a mixture of 8:2 petroleum ether: diethyl ether as eluent to obtain **59** (0.17 g, 0.21 mmol) as a pale yellow solid in 22% yield. **Mp** 80–82 ºC; **IR (NaCl)** ν_{max} 3313, 2939, 2837, 2359, 1818 cm^{-1}; **Analysis**: Calcd.for $C_{45}H_{56}N_2O_{12}$: C, 66.16; H, 6.91; N, 3.43. Found: C, 66.12; H, 6.89; N, 3.40; **LRMS** (ES): m/z: (rel. intensity %) 839 ($[M+Na]^+$, 100) ; **HRMS** (ES^+): Calcul. for $C_{45}H_{56}N_2NaO_{12}^+$ $[M+Na]^+$ m/z: 839.3731, found m/z: 839.3728 **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.39 – 7.13 (m, 5H, **H2'' - H6''**), 6.73 (dd, *J* = 5.4, 1.3 Hz, 1H, **H6**), 6.57 (s, 1H, **C**H_{Ar}), 6.43 (dd, *J* = 15.9, 1.2 Hz, 1H, **H2'**), 6.20 (dd, *J* = 15.8, 5.5 Hz, 1H, **H1'**), 5.15 – 4.79 (m, 1H, **H3**), 3.98 (d, *J* = 20.8 Hz, 1H, **H11**), 3.89 (s, 3H, O**C**H_3), 3.85 (s, 3H, O**C**H_3), 3.81 (s, 3H, O**C**H_3), 3.75 (s, 3H, O**C**H_3), 3.70 (s, 3H, O**C**H_3), 3.59 (b.s, 3H, O**C**H_3), 3.46 (d, *J* = 20.0 Hz, 1H. **H11**), 3.03 (dd, *J* = 13.4, 4.7 Hz, 1H, **C**H_2-C3), 2.59 – 2.43 (m, 1H, **C**H_2-C3), 2.23 (s, 3H, **C**H_3), 2.14 (s, 3H, **C**H_3-C9), 1.54 (s, 9H, NCOO-C(**C**H_3)$_3$), 1.25 (b.s, 9H, OCOO-C(**C**H_3)$_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 165.2 (**C4**), 151.5 (**C**-OCH_3), 151.2 (O**C**OO), 150.9 (**C**-OCH_3), 150.4 (**C**-OCH_3), 149.9 (N**C**OO), 148.8 (**C**-OCH_3), 146.6 (**C**-OCH_3), 145.8 (**C**-OCH_3), 136.4 (**C1''**), 131.2 (**C2'**), 128.5 (**C3'', C5''**), 127.8 (**C4''**), 127.3 (**C11a**), 126.8 (**C2'', C6''**), 126.7 (**C1'**), 125.2 (**C10a**), 125.1 (**C1**), 124.8 (**C6a**), 124.3 (**C**-Ar), 119.9 (**C-Me**), 114.9 (**C9**), 112.2 (**C**H_{Ar}), 83.6 (NCOO-**C**$(CH_3)_3$), 81.9 (OCOO-**C**$(CH_3)_3$), 61.0, 60.8, 60.6, 60.3, 60.2 (5x**OC**H_3), 58.7 (**C3**), 55.9 (**OC**H_3), 48.9 (**C6**), 29.2 (**C**H_2-C), 27.9 (OCOO-C(**C**H_3)$_3$) , 27.7 (NCOO-C(**C**H_3)$_3$), 20.7 (**C11**), 9.7 (**C**H_3-C9), 9.6 (**C**H_3).

5.4.17. General procedure to obtain (±)-(3*R**, 1'*E*)-1-methoxy-4-oxo-6-styryl-3-benzyl-1,2,3,6,11,11*a*,-hexahydropyrazino[1,2-*b*]isoquinoline-2-carboxylate 62a–62c.



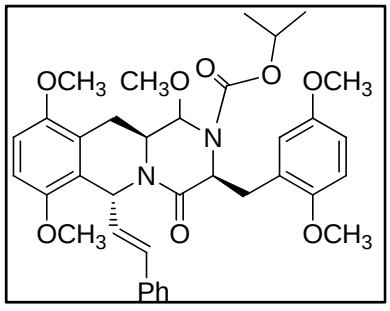
To compound **42b** or **43a** (1.0 eq) in dry THF (46 eq) (^{t}BuO)LiAlH (2.4 eq), was added under an argon atmosphere at room temperature and the reaction was stirred for 7.5 h. The reaction was poured into saturated solution of $NaHCO_3$ and filtered through celite. The celite was washed with DCM (3x 20 mL) and the mother liquor was extracted with DCM (2x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. The solution was concentrated *in vacuo* to obtain a pale yellow unstable solid which was used immediately in the next reaction, due to its unstability. To the pale yellow solid was added PPTS (0.15 eq) and dry methanol (46 eq) under an argon atmosphere at room temperature and the reaction was stirred for 76 h. The crude was quenched with a saturate solution of $NaHCO_3$, extracted with ethyl acetate (3x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to obtain compound **62a-62c** as unstable compounds**.**

5.4.17.1. Synthesis of (±)-(3*R**,6*S**, *11aS**, 1'*E*)-*tert*-butyl 1,7,8,10-tetramethoxy-3-(2,4,5-trimethoxy-3-methylbenzyl)-9-methyl-4-oxo-6-styryl-1,2,3,6,11,11a-hexahydropyrazino[1,2-*b*]isoquinoline-2-carboxylate 62a.



Obtained according to the general procedure **1.4.5** using compound **43a** (0.20 g, 0.28 mmol) as starting material, (^{t}BuO)LiAlH (0.18 g, 0.68 mmol) and dry THF (1.0 mL) as solvent. To the unstable compound **61b** was added PPTS (0.011 g, 0.043 mmol) and dry methanol (7.0 mL) and product **62a** (0.18 g, 0.25 mmol) was obtained as a yellow solid in 88% yield as a mixture of rotamers in $CDCl_3$, 25ºC; **IR(NaCl) ν_{max}** 2930, 2360, 1776, 1590 cm^{-1}. **^{1}H NMR** (250 MHz, MeOD) δ 7.34 – 7.10 (m, 5H, **H2'' - H6'',** 0.55H, **CH_{Ar}**), 6.89 (s, 0.45H, **CH_{Ar}**), 6.66 (d, *J* = 4.6 Hz, 1H, **H6**), 6.48 – 6.22 (m, 2H, **H1',H2'**), 5.27 (b.s, 1H, **H1**), 4.33 (dd, *J* = 4.9, 1.8 Hz, 1H, **H3**), 3.92 – 3.82 (m, 1H, **H11a**), 3.78, 3.76, 3.70, 3.69, 3.54, 3.45, 3,43, 3.31 (s,18H, 6xOC**H_3**, 3H, C1-OC**H_3**), 3.25 – 3.02 (m, 2H, **H11**, C**H_2**-C3), 2.92 (dd, *J* = 17.1, 4.9 Hz, 1H, C**H_2**-C3), 2.44 (dd, *J*=15.9,3.2 Hz, 1H, **H11**) 2.19, 2.16, 2.12, 2.10 (s, 6H, C**H_3**), 1.59, 1.52, 1.51 (s, 9H, C-(C**H_3**)$_3$); **^{13}C NMR** (63 MHz, MeOD) δ 169.7, 169.0* (**C4**, **C**O-O^{t}Bu), 153.5, 153.2 (**C**-OCH_3), 152.4 (**C**-OCH_3), 151.3, 151.2 (**C**-OCH_3), 150.2, 149.8 (**C**-OCH_3), 148.0, 147.7 (**C**-OCH_3), 147.1, 147.1 (**C**-OCH_3), 137.9, 137.6 (**C1''**), 133.6, 132.4 (**C2'**), 129.6 (**C3'', C5''**), 128.8, 128.7 (**C4''**), 128.0, 127.8 (**C1'**), 127.5, 127.4 (**C2'', C6''**), 127.2, 126.1, 125.8, 125.7, 125.4, 124.2, 123.4 (**C**-CH_3, **C**-Ar**, C9, C6a, C10**), 114.1, 113.6 (**C**H_{Ar}), 85.2, 82.7 (**C1**), 81.8 (**C**-$(CH_3)_3$), 61.2, 61.0, 60.6, 60.6, 60.5, 60.4, 60.3, 60.3, 60.2 (7xO**C**H_3), 59.1 (**C3**), 56.4, 56.3 (7xO**C**H_3), 54.1, 53.2 (**C11a**), 52.4, 50.9 (**C6**), 36.2, 33.0, 30.7, 30.7 (**C11**, **C**H_2-C3), 28.6, 28.2 (C-(**C**H_3)$_3$), 27.0, 25.4 (**C11**, **C**H_2-C3), 10.0, 9.7, 9.6, 9.5 (CH_3-**C9**, **C**H_3-Ar).

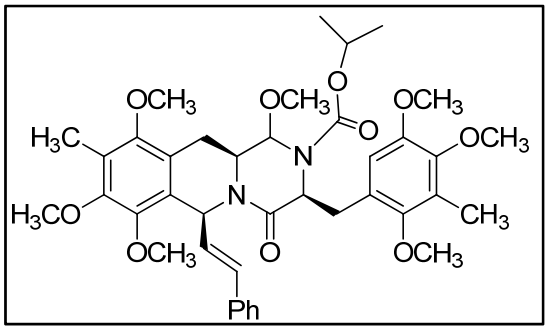
5.4.17.2. Synthesis of (±)-(3*R**,6*R**, *11aS*, *E*)-isopropyl1,7,10-trimethoxy-3-(2,5-dimethoxybenzyl)-4-oxo-6-styryl-1,2,3,6,11,11a-hexahydropyrazino[1,2-*b*]isoquinoline-2-carboxylate 62b.



Obtained according to the general procedure **4.4.17** using compound **42b** (0.20 g, 0.31 mmol) as starting material, (^{t}BuO)LiAlH (0.20 g, 0.76 mmol) and dry THF (2.0 mL) as solvent. To the unstable compound **61c** PPTS (0.011 g, 0.043 mmol) and dry methanol (7.0 mL) were added and product **62b** (0.18 g, 0.28 mmol) was obtained as a brown solid in 90% yield**. IR (NaCl) ν_{max}**

2930, 2360, 1776, 1590 cm^{-1}; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 3H, C**H$_{Ar}$**), 7.25 – 7.12 (m, 3H, C**H$_{Ar}$**), 6.76 – 6.59 (m, 3H, C**H$_{Ar}$**), 6.46 (s, 1H, **H2'**), 6.33 (m, 2H, C**H$_{Ar}$**), 6.27 (dd, *J* = 7.5, 2.2 Hz, 1H, **H1'**), 5.34 – 5.02 (m, 1H, OC**H**$(CH_3)_2$), 4.55 (s, 1H, **H1**), 3.99 (dd, *J* = 13.5, 5.0 Hz, 1H, **H11a**), 3.82 – 3.69 (m, 1H, **H3**), 3.80 (s, 3H, OC**H$_3$**), 3.85 (s, 6H, 2xOC**H$_3$**), 3.59 – 3.53 (m, 1H, **H11**), 3.35 (s, 3H, OC**H$_3$**), 3.27 (s, 3H, OC**H$_3$**), 3.15 (d, *J* = 16.0 Hz, 1H, **H11**), 2.31 (dd, *J* = 16.7, 3.4 Hz, 1H, C**H$_2$**-C3), 1.44 – 1.36 (m, 6H, OCH(C**H$_3$**)$_2$), 1.08 (m, 1H, C**H$_2$**-C3); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 166.6 (**C4**), 152.9, 152.4, 151.2, 150.0, 144.5 (4x**C**-OCH_3, ***C**OOCH$(CH_3)_2$), 137.3 (**C1''**), 130.4 (**C2'**), 128.5* **(C3'', C5'')**, 127.4, 127.2 (**C1', C4''**), 126.6* (**C2'', C6''**), 124.3, 124.88, 120.9 (**C7a, C10a, C1'''**), 113.4, 110.9, 107.9, 107.6 (**C8, C9, C3''', C4'''**), 83.2 (**C1**), 69.9 (O**C**H$(CH_3)_2$), 58.0 (**C11a**), 55.7, 55.6, 55.4, 55.4 (4x O**C**H_3), 55.1 (**C3**), 51.1 (**C6**), 50.4 (C1-O**C**H_3), 26.4, 26.3 (C**H$_2$**-C3, **C11**), 22.5 (OCH(C**H$_3$**)$_2$).

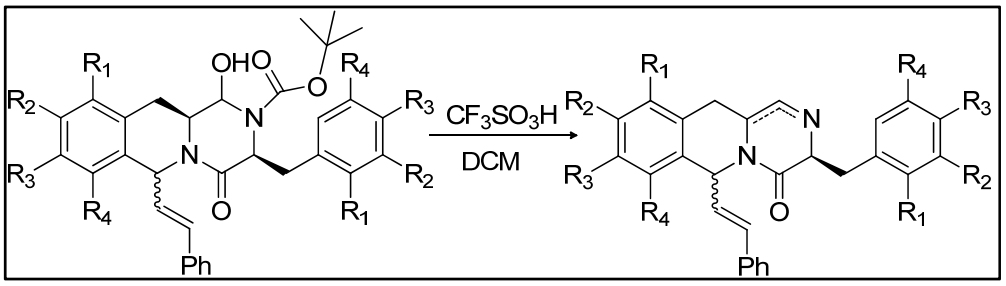
5.4.17.3. Synthesis of (±)-(3*S**,6*S**, *11aS**,*E*)-isopropyl 1,7,8,10-tetramethoxy-9-methyl-3-(2,4,5-trimethoxy-3-methylbenzyl)-4-oxo-6-styryl-1,2,3,6,11,11a-hexahydropyrazino[1,2-*b*]isoquinoline-2-carboxylate 62c.



Obtained according to the general procedure **4.3.17** using compound **43a** (0.20 g, 0.28 mmol) as starting material, (^{t}BuO)LiAlH (0.18 g, 0.68 mmol) and dry THF (2.0 mL) as solvent. To the unstable compound **61d** was added PPTS (0.011 g, 0.043 mmol) and anhydrous methanol (7.0 mL) and product **62c** (0.18 g, 0.25 mmol) was obtained as a brown solid in 90% yield as a mixture of rotamers 1:1 in $CDCl_3$, 25ºC. **IR (NaCl) ν_{max}** 2920, 2260, 1776, 1490 cm^{-1}; **^{1}H NMR** (250 MHz, MeOD) δ 7.32 – 7.13 (m, 5H, **H2'' - H6''**), 6.90 (d, *J* = 4.4 Hz, 0.5H, **H6**), 6.69 (d, *J* = 4.4 Hz, 0.5H, **H6**), 6.25 – 5.98 (m, 3H, **CH**-Ar, **H1', H2'**), 5.34-5.09 (m, 1H, **CH**-^{i}Pr), 4.94 (m,1H, **H1**), 4.62 – 4.28* (m, 1H, **H3**), 4.20 – 4.02* (m, 1H, **H11a**), 3.85, 3.79, 3.77, 3.71, 3.70, 3.68, 3.63, 3.62, 3.54, 3.52, 3.51, 3.46, 3.45, 3.31, 3.30* (s, 21H, 7xO**CH$_3$,** 0.6H, C**H$_2$**-C3), 3.27 – 2.82* (m, 3H, C**H$_2$**-C3**, H11**), 2.47* (dd, *J* = 15.9, 3.3 Hz, 0.4H, C**H$_2$**-C3), 2.20, 2.17, 2.11 (s, 6H, C**H$_3$**), 1.40 – 0.65 (m, 6H, CH-(C**H$_3$**)$_2$); **^{13}C NMR** (63 MHz, MeOD) δ 169.4, 168.8 (**C4**), 153.4, 153.2, 153.2, 153.1, 152.4, 151.2, 151.1, 150.2, 150.1, 149.8, 147.9, 147.7, 147.1, 147.0 (7x**C**-OCH_3), 137.9, 137.6 (**C1''**), 133.7, 132.5 (**C2'**), 129.6, 129.5 (**C2'', C3'', C5'', C6''**), 128.8, 128.7, 128.0, 127.8, 127.5, 127.4 (**C2'', C3'', C5'', C6''),** 127.2, 127.2, 126.06, 125.8 (**C**-CH_3, **C9**), 125.7, 125.4 (**C6a**), 124.1, 123.7 (**C**-Ar), 113.9, 113.4 (**CH$_{Ar}$**), 84.5, 84.5 (**C1**), 75.9, 70.7 (**CH**-$(CH_3)_2$), 66.8, 61.3, 61.0, 60.6, 60.5, 60.4, 60.4, 60.3, 60.2, (7xO**CH$_3$**), 59.0, 58.3 (**C3**),

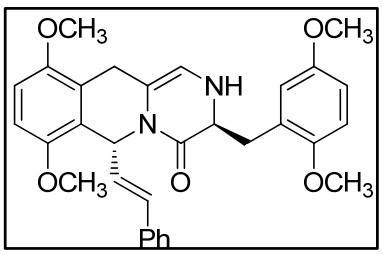
56.5, 56.2, 56.1 (7xO**C**H_3), 54.1, 53.2 (**C11a**), 52.6, 50.9 (**C6**), 36.1, 35.2 (**C**H_2-C3), 30.7, 30.0 (**C11**), 27.0, 25.3, 22.5, 22.3, 22.2, 22.0 (CH-(**C**H_3)$_2$), 10.0, 9.9, 9.8, 9.7 (2x**C**H_3).

5.4.18. General procedure to obtain 3-benzyl-6-styrylterahidropyrazino[1,2-*b*]isoquinolin-4(3*H*)-one 67–68.



To compound **61a**, **61b** or **61d** (1.0 eq) in dry DCM (4.0–14.0 eq) triflic acid (1-20 eq) was added and the resulting solution was stirred for 1 – 2 h between -10–25 ºC. The crude was quenched with a saturate solution of $NaHCO_3$, extracted with ethyl acetate (3x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. After purification by flash column chromatography on silica gel compound **67–68** were obtained.

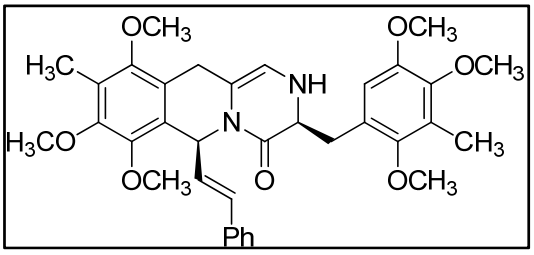
5.4.18.1. Synthesis of (±)-(3*S**,6*R**,*E*)-3-(2,5-dimethoxybenzyl)-7,10-dimethoxy-6-styryl-2,3,6,11-terahidrohydropyrazino[1,2-*b*]isoquinolin-4-one 67a.



Obtained according to the general procedure **4.3.18** using compound **61a** (0.54 g, 0.85 mmol) as starting material, triflic acid (0.5 mL, 5.73 mmol) and anhydrous DCM (1.0 mL) as solvent.at room temperature for 1.5 h. Purification by flash column chromatography on silica gel using 2:8 petroleum ether: diethyl ether as eluent afforded product **67a** (0.17 g, 0.34 mmol) as an orange solid in 40% yield. **Mp** 92–93 ºC; **IR (NaCl) ν_{max}** 2930, 1693, 1625 cm^{-1}; **Analysis**: Calcd.for $C_{31}H_{32}N_2O_5$: C, 72.64; H, 6.29; N, 5.47. Found: C, 72.46; H, 6.44; N, 5.40; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.34 – 7.16 (m, 5H, C**H$_{Ar}$**), 6.82 – 6.66 (m, 6H, **H8, H9, H3''', H4''', H6''', H6**), 6.37 (d, *J* = 15.9 Hz, 1H, **H2'**), 6.24 (dd, *J* = 15.8, 5.6 Hz, 1H, **H1'**), 6.01 (s, 3H, **H1**), 4.06 (dd, *J* = 10.1, 4.3 Hz, 1H, **H3**), 3.90 – 3.68 (m, 12H, 4xOC**H$_3$**), 3.64

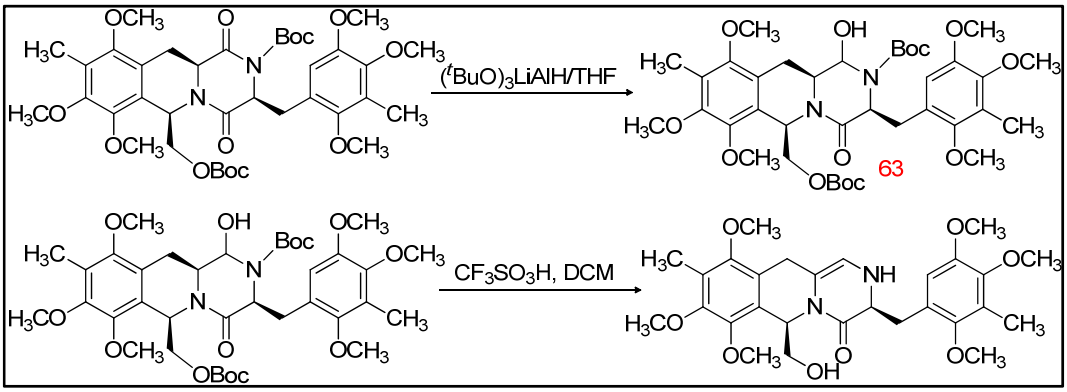
(s, 2H, **H11**), 3.58 – 3.47 (m, 1H, C**H**$_2$-C3), 2.90 (dd, *J* = 13.6, 10.0 Hz, 1H, C**H**$_2$-C3).; ^{13}**C NMR** (63 MHz, $CDCl_3$) δ 167.98 (**C4**), 153.53, 152.07, 149.61, 148.18 (4x**C**-OCH_3), 136.77 (**C1''**), 133.93 (**C11a**), 130.51 (**C2'**), 128.38* (**C2'', C6''**), 127.52 (**C4''**), 127.22** (**C6a, C10a**), 126.70* (**C3'', C5''**), 125.56 (**C1'**), 120.57, 119.83** (**C1'''**), 116.74 (**C6''**), 112.68, 111.52, 109.98, 109.32 (**C8, C9, C3'', C4''**), 98.98 (**C1**), 60.84 (**C3**), 56.01, 55.91, 55.68, 55.61 (4xO**C**H_3), 49.08 (**C6**), 47.00 (**C11**), 32.87 (**C**H_2-C3).

5.4.18.2. Synthesis of (±)-(3*S**,6*S**,1'*E*)-7,8,10-trimethoxy-9-methyl-6-styryl-3-(2,4,5-trimethoxy-3-methylbenzyl)-2,3,6,11-tetrahydropyrazino[1,2-*b*]isoquinolin-4-one 67c.



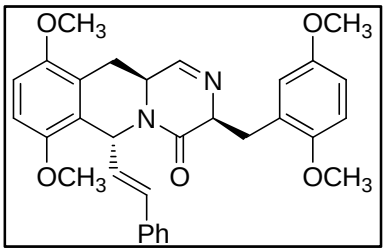
Obtained according to the general procedure **4.4.18** using compound **61b** (0.22 g, 0.30 mmol) as starting material, triflic acid (0.039 mL, 0.45 mmol) and dry DCM (0.11 mL) as solvent at -20 ºC for 2 h. Purification by flash column chromatography on silica gel using 5:5 diethyl ether: ethyl acetate as eluent afforded product **67c** (0.13 g, 0.21 mmol) as a yellow solid in 70% yield. **Mp** 93–95 ºC; **IR (NaCl) ν_{max}** 2940, 2359, 1646 cm^{-1}; **Analysis**: Calcd.for $C_{35}H_{40}N_2O_7$: C, 69.98; H, 6.71; N, 4.66 Found: C, 69.90; H, 6.61; N, 4.76.; ^{1}**H NMR** (250 MHz, $CDCl_3$) δ 7.35-7.09 (m, 6H, **NH, H2'' - H6''**), 6.63 (s, 1H, C**H**$_{Ar}$), 6.60 (d, *J* = 6.1 Hz, 1H, **H6**), 6.38 (d, *J* = 15.9 Hz, 1H, **H2'**), 6.23 (dd, *J* = 15.8, 6.1 Hz, 1H, **H1'**), 5.83 (s, 1H, **H1**), 4.00 (dd, *J* = 9.2, 3.8 Hz, 1H, **H3**), 3.84 (s, 3H, OC**H**$_3$), 3.81 (s, 3H, OC**H**$_3$), 3.74 (s, 3H, OC**H**$_3$), 3.73 (s, 3H, OC**H**$_3$), 3.70 (s, 3H, OC**H**$_3$), 3.66 (s, 3H, OC**H**$_3$), 3.61 (b.s, 2H, **H11**), 3.46 (dd, *J* = 13.7, 3.6 Hz, 1H, C**H**$_2$-C3), 2.93 (dd, *J* = 13.8, 9.2 Hz, 1H, C**H**$_2$-C3), 2.19 (s, 6H, C**H**$_3$); ^{13}**C NMR** (63 MHz, $CDCl_3$) δ 167.9 (**C4**), 151.1, 150.8, 149.5, 149.4, 146.7, 145.9 (6xO**C**H_3), 136.6 (**C1''**), 133.2 (**C6a**), 131.4 (**C2'**), 128.5 (**C3'', C5''**), 127.8 (**C4''**), 126.8 (**C2'', C6''**), 126.1 (**C1'**), 125.6 , 125.4 (2x**C**-CH_3), 125.1 (**C**-Ar), 122.3 (**C10a**), 119.7 (**C11a**), 110.8 (**C**H_{Ar}), 99.4 (**C1**), 61.6, 61.4, 60.9, 60.5, 60.2, 60.2, 55.8 (6xO**C**H_3, **C3**), 49.6 (**C6**), 47.2 (**C11**), 32.6 (**C**H_2-C3), 9.8, 9.4 (2x**C**H_3).

5.4.19. Synthesis of (±)-(3*S**,6*R**,*E*)-6-hydroxymethyl-7,8,10-trimethoxy-9-methyl-3-(2,4,5-trimethoxy-3-methylbenzyl)-2,3,6,11-tetrahydropyrazino[1,2-*b*]isoquinolin-4-one 67b.



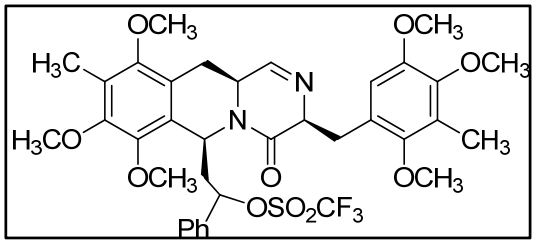
To compound **50** (0.068 g, 0.09 mmol), (^{t}BuO)LiAlH (0.14 g, 0.54 mmol) and THF (1.0 mL) was added at room temperature under an argon atmosphere and the reaction was stirred for 5 h. The mixture was poured into a saturated solution of $NaHCO_3$ and was filtered through celite. The celite was washed with DCM (3x 20 mL) to extract the compound **63**, and the mixture was extracted with DCM (2x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. The solution was concentrated *in vacuo* to obtain a pale yellow solid which was used immediately in the next reaction, due to its unstability. To the pale yellow solid anhydrous DCM (0.076 mL) and triflic acid (0.076 mL, 0.87 mmol) was added under an argon atmosphere at room temperature and the reaction was stirred for 1 h. The crude was quenched with a saturate solution of $NaHCO_3$, extracted with DCM (3x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to obtain compound **67b** (0.039 g, 0.074 mmol) as a brown solid in 82% yield. **Mp** 88–90 ºC; **IR (NaCl)** ν_{max} 2940, 1653 cm^{-1}; **Analysis**: Calcd.for $C_{28}H_{36}N_2O_8$: C, 63.62; H, 6.86; N, 5.30 Found: C, 63.71; H, 6.80; N, 5.15.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.62 (s, 1H, C**H$_{Ar}$**), 6.10 (t, *J* = 6.4 Hz, 1H, **H6**), 5.80 (s, 1H, **H1**), 4.06 (dd, *J* = 9.2, 4.0 Hz, 1H, **H3**), 3.90-3.65 (m, 2H, O**H**, N**H**)3.90 (s, 3H, OC**H$_3$**), 3.79(s, 3H, OC**H$_3$**), 3.74 (s, 3H, OC**H$_3$**), 3.72 (s, 3H, OC**H$_3$**), 3.67 (s, 3H, OC**H$_3$**), 3.65 (s, 3H, OC**H$_3$**), 3.61 – 3.51 (m, 4H, 2x**H11**, 2x**H1'**), 3.47 – 3.37 (dd, J= 14.7, 4.6 Hz, 1H, C**H$_2$**-C3), 2.91 (dd, *J* = 13.7, 9.3 Hz, 1H, C**H$_2$**-C3), 2.17 (s, 3H, C**H$_3$**), 2.16 (s, 3H, C**H$_3$**).; **^{13}C NMR** (63 MHz, $CDCl_3$) δ 170.0 (**C4**), 151.1, 150.6, 149.5, 149.4, 146.8, 145.9 (6xO**C**H_3), 133.0, 125.6, 125.6, 125.2, 120.2, 119.9 (**C$_{Ar}$**-CH_3, **C$_{Ar}$**, **C6a, C9, C10a, C11a**), 110.9 (**C**H-Ar), 99.4 (**C1**), 65.0 (**C1'**), 61.4, 61.4, 60.9, 60.8, 60.3, 60.2, 55.9 (6xO**C**H_3**, C3)**, 50.6 (**C6**), 46.7 (**C11**), 32.4 (**CH_2**-C3), 9.8, 9.4 (2x CH_3).

5.4.19.1. Synthesis of (±)-(3S*,6*R**, *11aS**,*E*)-3-(2,5-dimethoxybenzyl)-7,10-dimethoxy-6-styryl-11,11a-dihydro-6*H*-pyrazino[1,2-*b*]isoquinolin-4(3*H*)-one 68a.



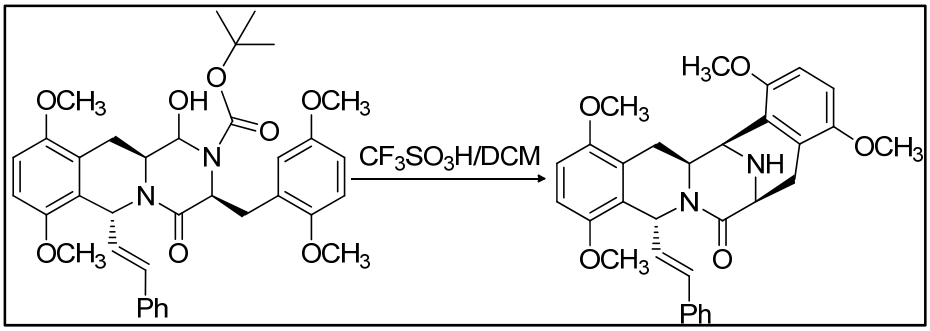
Obtained according to the general procedure **4.3.19** using compound **61a** (0.54 g, 0.85 mmol) as starting material, triflic acid (0.5 mL, 5.73 mmol) and dry DCM (1.0 mL) as solvent.at room temperature for 1.5 h. Purification by flash column chromatography on silica gel using 2:8 petroleum ether:diethyl ether as eluent afforded product **68a** (0.087 g, 0.17 mmol) as an orange solid in 20% yield as a unstable product. **IR (NaCl) ν_{max}** 2930, 1720, 1650 cm^{-1}; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.72 (s, 1H, **H1**), 7.25 – 7.13 (m, 3H, C**H$_{Ar}$**), 6.86 – 6.80 (m, 2H, C**H$_{Ar}$**), 6.72* (s, 2H, **H8, H9**), 6.67* (s, 2H, **H3’’’, H4’’’**), 6.53 (dd, *J* = 8.8, 3.1 Hz, 1H, **H2’**), 6.47 (d, *J* = 2.8 Hz, 1H, **H6’’’**), 6.42 (d, *J* = 8.9 Hz, 1H, **H1’**), 6.07 (d, *J* = 6.8 Hz, 1H, **H6**), 4.73 – 4.65 (m, 1H, **H11a**), 3.81 (s, 2.3H, OC**H$_3$**), 3.78 (s, 0.7H, OC**H$_3$**), 3.70 (s, 2H, OC**H$_3$**), 3.68 (s, 0.5H, OC**H$_3$**), 3.57 – 3.51 (m, 1H, **H3**), 3.37 (s, 2H, OC**H$_3$**), 3.33 (s, 1H, OC**H$_3$**), 3.31 (s, 2.0H, OC**H$_3$**), 3.29 (s, 1H, OC**H$_3$**), 2.71 – 2.59 (m, 1H, C**H$_2$**-C3), 2.07 (d, *J* = 17.9 Hz, 1H, **H11**), 1.98 (dd, *J* = 13.7, 3.9 Hz, 1H, C**H$_2$**-C3), 0.93 (d, *J* = 17.4 Hz, 1H, **H11**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 163.3 (**C4**), 159.4 (**C1**), 152.8, 152.4, 151.2, 148.3 (4x**C**-OCH_3), 138.2 (**C1’’**), 130.0* (**C6a**), 128.8, 128.7 (**C2’’, C3’’, C5’’, C6’’**), 127.5 (**C4’’**), 125.4 (**C10a**), 121.1* (**C1’’’**), 116.4 (**C6’’’**), 113.7 (**C2’**), 111.3 (**C1’**), 108.8, 108.6 (**C8, C9, C3’’’, C4’’’**), 62.8 (**C11a**), 56.0, 55.7, 55.5, 55.2 (4xO**C**H_3), 53.5 (**C3**), 47.8 (**C6**), 39.6 (**C**H_2-C3), 30.2 (**C11**).

5.4.19.2. Synthesis of (±)-(3*S,6*S**, *11aS**)-1-phenyl-2-(7,8,10-trimethoxy-9-methyl-4-oxo-3-(2,4,5-trimethoxy-3-methylbenzyl)-3,4,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinolin-6-yl)ethyltrifluoromethanesulfonate 68b.**



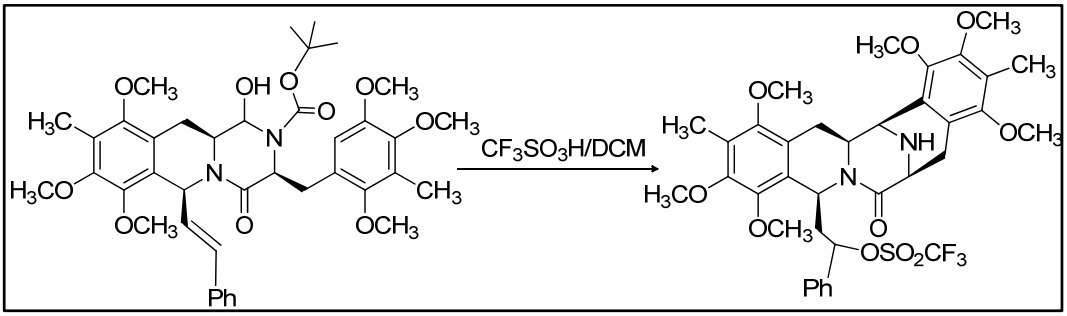
Obtained according to the general procedure **4.3.19** using compound **61b** (0.20 g, 0.28 mmol) as starting material, triflic acid (0.5 mL, 5.7 mmol) and dry DCM (0.2 mL) as solvent at room temperature for 1 h. Purification by flash column chromatography on silica gel using of 5:5 diethyl ether: ethyl acetate as eluent afforded product **68b** (0.037 g, 0.06 mmol) as a brown oil in 21% yield as a unstable compound. **IR (NaCl) ν_{max}** 2930, 1778 cm^{-1}; **^{1}H NMR** (250Hz, $CDCl_3$) δ 7.63 – 7.55 (m, 1H, **H4''**), 7.38 – 7.07 (m, 4H, **H2'' - H6''**), 6.60 (s, 1H, C**H**$_{Ar}$), 6.32 (d, *J* = 5.9 Hz, 1H, **H6**), 4.80 – 4.63* (m, 1H, **H3**), 4.05 (s, 3H, OC**H$_3$**), 3.98 (s, 3H, OC**H$_3$**), 3.95 – 3.86* (m, 4H, **H1,** 2x **H1', H2'**), 3.81 (s, 3H, OC**H$_3$**), 3.73 (s, 3H, OC**H$_3$**), 3.71 (s, 3H, OC**H$_3$**), 3.68 – 3.60* (m, 2H, 2x**H11**), 3.47 (s, 3H, OC**H$_3$**), 3.23* (dd, *J* = 13.5, 6.5 Hz, 1H, C**H$_2$**-C3), 3.08* (d, *J* = 16.6 Hz, 1H, C**H$_2$**-C3), 2.33 (s, 3H, C**H$_3$**), 2.24 (s, 3H, C**H$_3$**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.2 (**C4**), 159.1 (**C1**), 153.3, 151.4, 150.8 (3x**C**-OCH_3), 150.4, 149.4, 148.8, 147.4 (**C**F_3, *J* = 250 Hz), 146.5, 144.7, 141.2 (3x **C**-OCH_3), 130.4 (**C1''**), 129.1* (**C2'', C6''**), 127.7* (**C3'', C4'', C5''**), 125.3 (**C**-CH_3), 124.8, 124.8 (**C6a, C10a**), 124.4 (**C**-CH_3), 118.9 (**C**-Ar), 110.9 (**CH**$_{Ar}$), 77.4 (**C2'**), 62.8** (**C6**), 61.1, 61.0, 60.4, 60.1, 59.9, 55.0 (6x**OC**H_3), 52.8**, 48.9** (**C3, C11a**), 45.4, 37.8, 33.4 (**C**H_2-C3, **C11, C1'**) 9.8, 9.5 (2x**C**H_3).

5.4.20. Synthesis of (±)-(6*S**,9*R**,14a*S**,15*R**,1'*E*)-1,4,10,13-tetramethoxy-9-styryl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 69a.



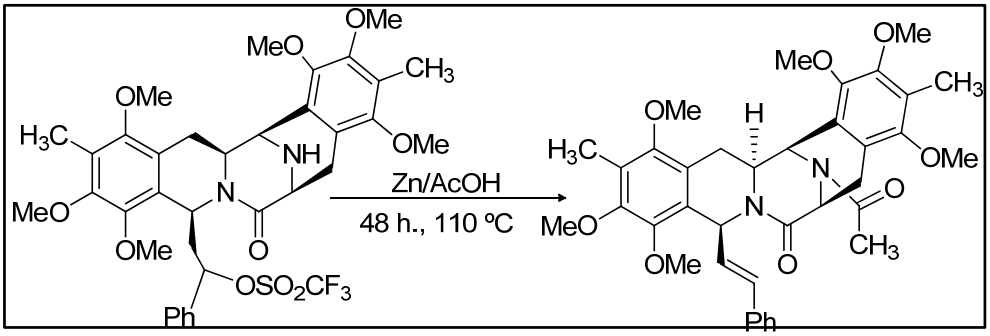
To a solution of **61a** (0.36 g, 0.57 mmol) in dry DCM (1.0 mL) triflic acid (1.0 mL, 0.011 mol) was added at room temperature and the reaction was stirred for 1 h. The crude was quenched with a saturate solution of $NaHCO_3$, extracted with DCM (3x 15 mL) was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and after purification by flash column chromatography on silica gel using ethyl acetate as eluent compound **69a** (0.059 g, 0.12 mmol) was obtained as a brown solid in 21% yield. **Mp** 110–111ºC; **IR (NaCl) ν_{max}** 3200, 2930, 1693, 1625 cm^{-1}; **Analysis**: Calcd.for $C_{31}H_{32}N_2O_5$: C, 72.64; H, 6.29; N, 5.47. Found: C, 72.56; H, 6.48; N, 5.50.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.64 – 6.07 (m, 11H, **CH_{Ar}, H9, H1', H2'**), 5.48 (s, 1H. **CH_{Ar}**), 4.44 – 4.27 (m, 1H, **H15**), 4.05 – 3.95 (s, 1H, **H14a**), 3.87 – 3.68 (m, 12H, 4xOCH_3), 3.60 (s, 1H, **H6**), 3.42 – 3.36 (m, 1H, **H14**), 3.08 – 3.95 (m, 2H, **H5**), 2.10 – 1.78 (m, 1H, **H14**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 172.5 (**C7**), 153.6, 152.0, 151.4, 151.3 (4x**C**-OCH_3), 136.8 (**C1'''**), 128.4, 128.3 (**C2'', C3'', C5'', C6''**), 128.0 (**C4''**), 126.3, 123.9, 123.8, 120.8 (**C9a, C13a, C4a, C15a**), 117.6, 112.6, 111.5, 108.6, 108.5, 107.4 (**CH_{Ar}, C1', C2'**), 58.2 (**C6**), 55.9, 55.8, 55.7, 55.6, 55.5, 55.3 (4xOCH_3, **C9, C14a**), 53.8 (**C15**), 33.3 (**C14**), 23.4 (**C5**).

5.4.21. Synthesis of (±)-(6*S**,9*S**,14a*S**,15*R**)-2-(1,2,4,10,11,13-hexamethoxy-3,12-dimethyl-7-oxo-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-9-yl)-1-phenylethyl trifluoromethanesulfonate 69b.



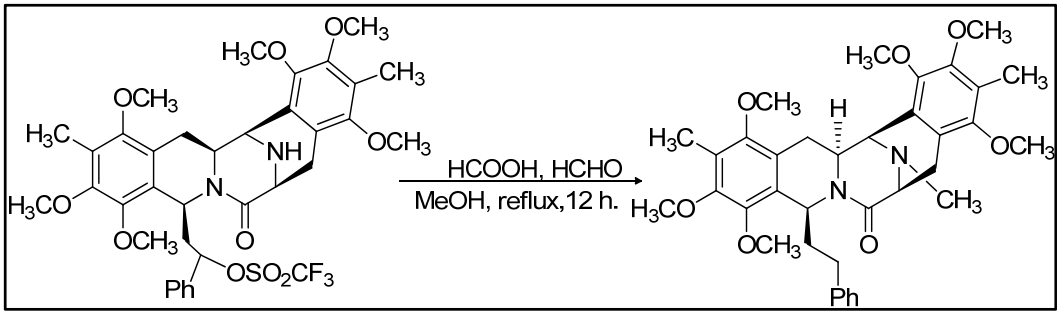
To a solution of **61b** (0.2 g, 0.27 mmol) in dry DCM (1.0 mL) triflic acid (0.7 mL, 0.008 mol) was added at room temperature and the reaction was stirred for 1 h. The crude was quenched with a saturate solution of $NaHCO_3$ and extracted with DCM (3x 15 mL) was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and after purification by flash column chromatography on silica gel using a mixture of 95:5 ethyl acetate: methanol as eluent compound **69b** (0.050 g, 0.067 mmol) was obtained as a brown solid in 25% yield. **Mp** 138–140 ºC; **IR (NaCl)** ν_{max} 3318, 2940, 1636 cm^{-1}; **Analysis**: Calcd.for $C_{36}H_{41}N_2SO_9$: C, 57.59; H, 5.50; N, 3.73, S, 4.27. Found: C, 57.46; H, 5.40; N, 3.76, S, 4.20; ^{1}**H NMR** (250 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 6.7, 2.9 Hz, 2H, **H2'', H6''**), 7.44 – 7.37 (m, 3H, **H3'',H4'',H5''**), 7.17 – 6.99 (m, 1H, **NH**), 5.56 (dd, *J* = 12.1, 2.3 Hz, 1H, **H2'**), 5.07 (dd, *J* = 11.0, 3.6 Hz, 1H, **H6**), 4.54 (s, 1H, **H15**), 4.52 (s, 1H, **H14a**), 3.91-3.86 (m,1H, **H6**), 3.86 (s, 3H, OC**H$_3$**), 3.82 (s, 3H, OC**H$_3$**), 3.79 (s, 3H, OC**H$_3$**), 3.76 (s, 3H, OC**H$_3$**), 3.72 (s, 3H, OC**H$_3$**), 3.65 (s, 3H, OC**H$_3$**), 3.30 – 2.98 (m, 5H, 2x**H14**, 2x**H5, H1'**), 2.76 – 2.60 (m, 1H, **H1'**), 2.19 (s, 3H, C**H$_3$**), 2.15 (s, 3H, C**H$_3$**); ^{13}**C NMR** (63 MHz, $CDCl_3$) δ 175.7 (**C7**), 152.4, 152.4, 150.5, 150.3, 146.3, 145.5 (6x **C**-OCH_3), 135.0 (**C1''**), 130.2 (**C4''**), 129.1 (**C3'',C5''**), 127.5 (**C2'', C6''**), 126.5, 126.2, 125.8, 123.0, 121.8, 121.0 (**C4a, C9a, C13a, C15a, C3, C12**),120.3 (q, *J* = 420 Hz, **C**F_3) 83.5 (**C2'**), 62.1 (**C6**), 61.0, 60.7, 60.4, 60.1, 60.1, 59.9 (6xO**C**H_3), 56.3 (**C9**), 50.8 (**C14a**), 49.0 (**C15**), 33.8 (**C1'**), 28.0, 27.8 (**C14, C5**), 9.4, 9.2 (2x**C**H_3).

5.4.22. Synthesis of (±)-(6*S**,9*S**,14a*S**,15*R**,1'*E*)-16-acetyl-1,2,4,10,11,13-hexamethoxy-3,12-dimethyl-9-styryl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 70.



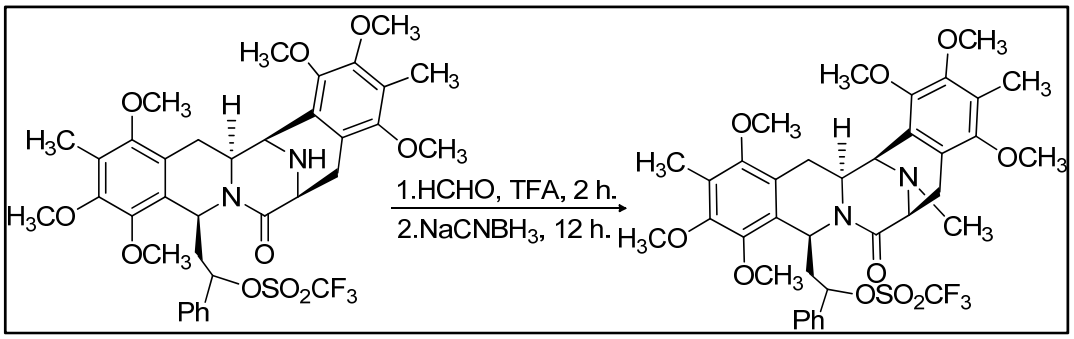
To a solution of **69b** (0.05 g, 0.065 mmol) in acetic acid (5.0 mL) Zn (0.05 mL, 0.008 mol) was added at 110 ºC and the reaction was stirred for 24 h. The crude was filtered to remove the Zn. The mother liquor was washed with a saturated solution of $NaHCO_3$ and extracted with DCM (3x 15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to obtain compound **70** (0.016 g, 0.025 mmol) as a brown solid in 40% yield as a mixture of rotamers in $CDCl_3$, 25ºC. **Mp** 110–112 ºC; **IR (NaCl) ν_{max}** 2933, 1650 cm^{-1}; **Analysis**: Calcd.for $C_{37}H_{42}N_2O_8$: C, 69.14; H, 6.59; N, 4.36. Found: C, 69.04; H, 6.51; N, 4.30.; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.31- 7.10 (m, 5H, **H2'', H3'', H4'', H5'', H6''**), 6.48 – 6.39 (m, 1H, **H2'**), 6.16 – 6.01 (m, 1H, **H1',** 0.8H, **H15**), 5.84 (d, *J* = 7.2 Hz, 1H, **H9**), 5.49 (dd, *J* = 5.3, 1.5 Hz, 0.27H, **H14a**), 5.31-5.30 (m, 0.2H, **H15**), 4.75 (dd, *J* = 5.4, 1.5 Hz, 0.83H, **H14a**), 3.88 – 3.87 (m, 3H, OC**H$_3$**), 3.79 (s, 3H, OC**H$_3$**), 3.76 (s, 3H, OC**H$_3$**), 3.75 (s, 3H, OC**H$_3$**), 3.72 (s, 3H, OC**H$_3$**), 3.67-3.66 (m, 3H, OC**H$_3$**), 3.51 – 3.16 (m, 3H, **H14, H5, H6**), 3.05 – 2.82 (m, 2H, **H14, H5**), 2.24 – 2.18 (m, 3H, COC**H$_3$**), 2.21 – 2.16 (m, 6H, C**H$_3$**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 170.8, 170.1 (**C7**), 168.4, 167.9 (**C**OCH_3), 152.8, 152.49 (**C**-OCH_3), 151.8, 151.6 (**C**-OCH_3), 150.6, 150.5 (**C**-OCH_3), 150.4, 150.0 (**C**-OCH_3), 146.7, 146.4 (**C**-OCH_3), 145.8, 145.1 (**C**-OCH_3), 137.0, 136.9 (**C1''**), 130.8, 130.7 (**C2'**), 129.3, 129.0 (**C1'**), 128.5, 128.4 (**C3'',C5''**), 127.8* (**C15a**), 127.5, 127.4 (**C4''**), 127.2* (**C4a**), 127.0, 126.9 (**C9a**), 126.7, 126.6 (**C2'', C6''**), 125.9*, 125.7* (**C13a**), 125.2, 125.1, 124.5, 124.4 (2x**C**-CH_3), 122.1*, 120.6* (**C13a, C15a**), 63.5, 63.3 (**C6**), 61.1, 61.0, 60.4, 60.3, 60.2, 60.1, 60.0, 58.9 (6xO**C**H_3), 56.0 (**C14a**), 54.9, 54.8 (**C9**), 52.4 (**C15**), 51.0 (**C14a**), 46.3 (**C15**), 31.4, 30.8 (**C14**), 26.2 (**C5**), 21.4, 21.0 (CO**C**H_3), 9.5, 9.5 (2x**C**H_3).

5.4.23. Synthesis of (±)-(6*S**,9*S**,14a*S**,15*R**)-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-9-phenethyl-5,6,9,14,14a,15-hexahydro-6,15-epiminoisoquino[3,2-*b*][3]benzazocin-7-one 71a.



To a solution **69b** (0.1 g, 0.13 mmol) in methanol (0.2 mL) formaldehyde 37% (0.2 mL, 0.0027 mol) was added and formic acid (0.14 mL, 0.036 mmol) and the reaction was stirred to reflux for 12 h. The crude was concentrated *in vacuo*, quenched with a saturate solution of $NaHCO_3$, extracted with DCM (3x 15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. After purification by flash column chromatography on silica gel using a mixture of 9:1 ethyl acetate:methanol as eluent, compound **71a** (0.045 g, 0.073 mmol) was obtained as a yellow solid in 56% yield. **Mp** 106–108 ºC; **IR (NaCl) ν_{max}** 2938, 2360, 1646, 1464 cm^{-1}; **Analysis**: Calcd.for $C_{36}H_{44}N_2O_7$: C, 70.11; H, 7.19; N, 4.54. Found: C, 70.12; H, 7.10; N, 4.44; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.31-7.16 (m, 5H, **H2'' - H6''**), 5.68 (dd, *J* = 6.6, 3.9 Hz, 1H, **H9**), 4.72 (dd, *J* = 10.2, 1.7 Hz, 1H, **H14a**), 4.26 (d, *J* = 1.6 Hz, 1H, **H15**), 3.97 – 3.87 (m, 1H, **H6**), 3.84 (s,3H, O**CH$_3$**), 3.82 (s,3H, O**CH$_3$**), 3.76 (s,3H, O**CH$_3$**), 3.73 (s,3H, O**CH$_3$**), 3.72 (s,3H, O**CH$_3$**), 3.69 (s,3H, O**CH$_3$**), 3.40 – 3.35 (m, 1H, **H14**), 3.13 – 2.87 (m, 4H, 2x **H2',** 2x**H5**), 2.61 (s, 3H, N-C**H$_3$**), 2.41– 2.20 (m, 2H, **H14, H1'**), 2.18 (s, 3H, C**H$_3$**),2.15 (s, 3H, C**H$_3$**), 1.92 (ddd, *J*= 14.6, 6.7, 2.0, 1H, **H1'**);**^{13}C NMR** (63 MHz, $CDCl_3$) δ 174.9 (**C7**), 152.4, 151.5, 150.5, 150.0, 146.0, 145.6, 144.6 (6x**C**-OCH_3, **C1''**), 129.4, 128.5** **(C13a, C15a**), 128.3* (**C2'', C6''**), 127.0 (**C4''**), 125.9** (**C3**), 125.8* (**C3'', C5''**), 124.5, 124.0 , 120.3** (**C12, C13a, C15a**), 71.2 (**C14a**) , 61.0, 60.9, 60.3, 60.2, 60.1, 60.0, 59.5 (6xO**CH$_3$, C6**), 56.2 (**C15**), 50.3 (**C9**), 49.2 (**C1'**), 40.3 (N**CH$_3$**), 31.1 (**C5**), 29.8 (**C14**), 20.6 (**C2'**), 9.5, 9.4 (**CH$_3$**-C3, **CH$_3$**-C12).

5.4.24. Synthesis of 2-(1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-7-oxo-6,7,9,14,14a,15-hexahydro-5*H*-6,15-epiminobenzo[4,5]azocino[1,2-*b*]isoquinolin-9-yl)-1-phenylethyl trifluoromethanesulfonate 71b.



To a solution of **69b** (0.1 g, 0.13 mmol) in methanol (0.6 mL) formaldehyde 37% (0.07 g, 0.85 mmol) and TFA (1.6 eq) were added at room temperature and the reaction was stirred for 2 h. To this solution sodium cyanoborohydride (0.048 g, 0.78 mmol) was added at room temperature and this mixture was stirred for 12 h more. The mixture was quenched with a saturate solution of $NaHCO_3$, extracted with DCM (3x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography using diethyl ether as eluent to obtain **71b** (0.082 g, 0.11 mmol) as a pale yellow solid in 81% yield. **Mp** 110–112 ºC; **IR (NaCl) ν_{max}** 2933, 1650 cm^{-1}; **Analysis**: Calcd.for $C_{37}H_{43}N_2S$: C, 58.11; H, 5.67; N, 3.66; S, 4.19. Found: C, 58.01; H, 5.67; N, 3.59; S, 4.21; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.44 – 7.26 (m, 5H, **H2'' - H6''**), 5.33 (d, *J* = 3.5 Hz, 1H, **H2'**), 5.11 (dd, *J* = 12.2, 2.1 Hz, 1H, **H9**), 4.59 (dd, *J* = 11.4, 7.2 Hz, 1H, **H6**), 3.80 (s, 6H, 2x OCH_3), 3.77 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.52 – 3.39 (m, 1H, **H14a**), 3.24 (m, 1H, **H1'**), 3.01 (m, 2H, **H15, H14**), 2.76 – 2.64 (m, 3H, **H14, H5, H1'**), 2.37 (s, 3H, NCH_3), 2.22 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.05 – 1.92 (m, 1H, **H5**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 152.0 (**C7**), 151.2, 149.7, 149.1, 147.0, 146.5, 143.8 (6x**C**-OCH_3), 130.4 (**C1''**), 128.5* (**C2'', C6''**), 127.6 (**C4''**), 127.2, 127.1 (**C13a, C15a**), 126.3* (**C3'',C5''**), 125.7** (**C4a**), 123.4, 123.3 (**C3, C12**), 122.9** (**C9a**), 80.0 (**C2'**), 73.7 (**C9**), 60.6, 60.5, 60.2, 60.2, 60.1, 59.7 (6xOCH_3), 57.7 (**C14a**), 57.1 (**C14a, C15**), 53.7 (**C6**), 41.8 (NCH_3), 38.3 (**C5**), 22.8 (**C1'**), 15.2 (**C14**), 9.5, 9.3 (2xCH_3).

6. Capítulo VI. Conclusiones.

En el trabajo presentado hemos conseguido alcanzar un método suave para la obtención, en un sólo paso, de tetrahidroisoquinolinas por medio de una variante de la reacción de Pictet-Spengler a través de una α-amidosulfona. Se propone un mecanismo alternativo al bibliográfico para la formación de dicho intermedio.

La aplicación de este nuevo método a la síntesis del esqueleto de análogos de alcaloides del grupo de las saframicinas consigue la ciclación del anillo B de los sistemas pentacíclicos en una estrategia basada en la simetría que mantiene el orden de formación de los anillos ACE-D-B. La formación del anillo B requiere introducir una cadena espaciadora en la posición C9 que disminuya la tensión en el intermedio α-amidosulfona. El pentaciclo resultante se obtuvo inicialmente como una mezcla de dos diastereoisómeros, la cual puede ser dirigida hacia la estereoquímica de los compuestos de origen natural mediante un incremento en la concentración del material de partida, o bien con la manipulación de los sustituyentes de los anillos A y E.

La incorporación en C6, del triciclo, de un grupo estirilo no sólo ofrece la cadena espaciadora necesaria para la ciclación del anillo B sino que proporciona la posibilidad de funcionalizar, mediante una ruptura oxidativa, la posición C9 del pentaciclo.

Cuando la estrategia aplicada mantiene el orden de síntesis de los anillos ACE-B-D, se consigue también una notable disminución en el número de pasos respecto a los métodos bibliográficos. Esta ruta se basa en una reacción regio y diastereoselectiva que genera el anillo B mediante el empleo de intermedios de α-amidosulfona. La diastereoselección de esta reacción está regida por el sustituyente en C6 y la sustitución del anillo A y E, siendo crucial la interacción entre el anillo A y el sustituyente estirilo en C6 en el intermedio de α-amidosulfona para rendir la disposición espacial de los compuestos naturales. La ciclación del anillo D requiere el uso de superácidos en estructuras que dirijan el anillo E a una disposición cercana a la posición C1 para lo que resulta primordial poder establecer una interacción entre el anillo E y el sustituyente en C9.

Por otro lado, el estudio SAR realizado mediante el uso de compuestos conteniendo una función urea incorporada a un núcleo de tetrahidroisoquinolina como antagonistas de la proteína de transmembrana TRPM8, implicada en el transporte de Ca^{2+} al citosol, arroja datos prometedores sobre la inducción de apoptosis en células tumorales en las que este canal está sobreexpresado. De la misma forma, estructuras de tetrahidropirazinoisoquinolinas han resultado potentes antagonistas de estos canales, siendo de destacar la importancia de la sustitución de los grupos metoxi en R_1 y R_4, en los anillos aromáticos A y E.

7. Capítulo VII. Conclusions.

Conclusions.

In the present thesis we have developed a one-pot reaction leading to tetrahydroisoquinolines under mild conditions of temperature and acidity and avoiding the use of strong Lewis or Brønsted acids, which are commonly needed in previously described Pictet-Spengler reactions, and proceeding via α-amidosulfone intermediates. We propose an alternative to the literature mechanism that explains the formation of these intermediates.

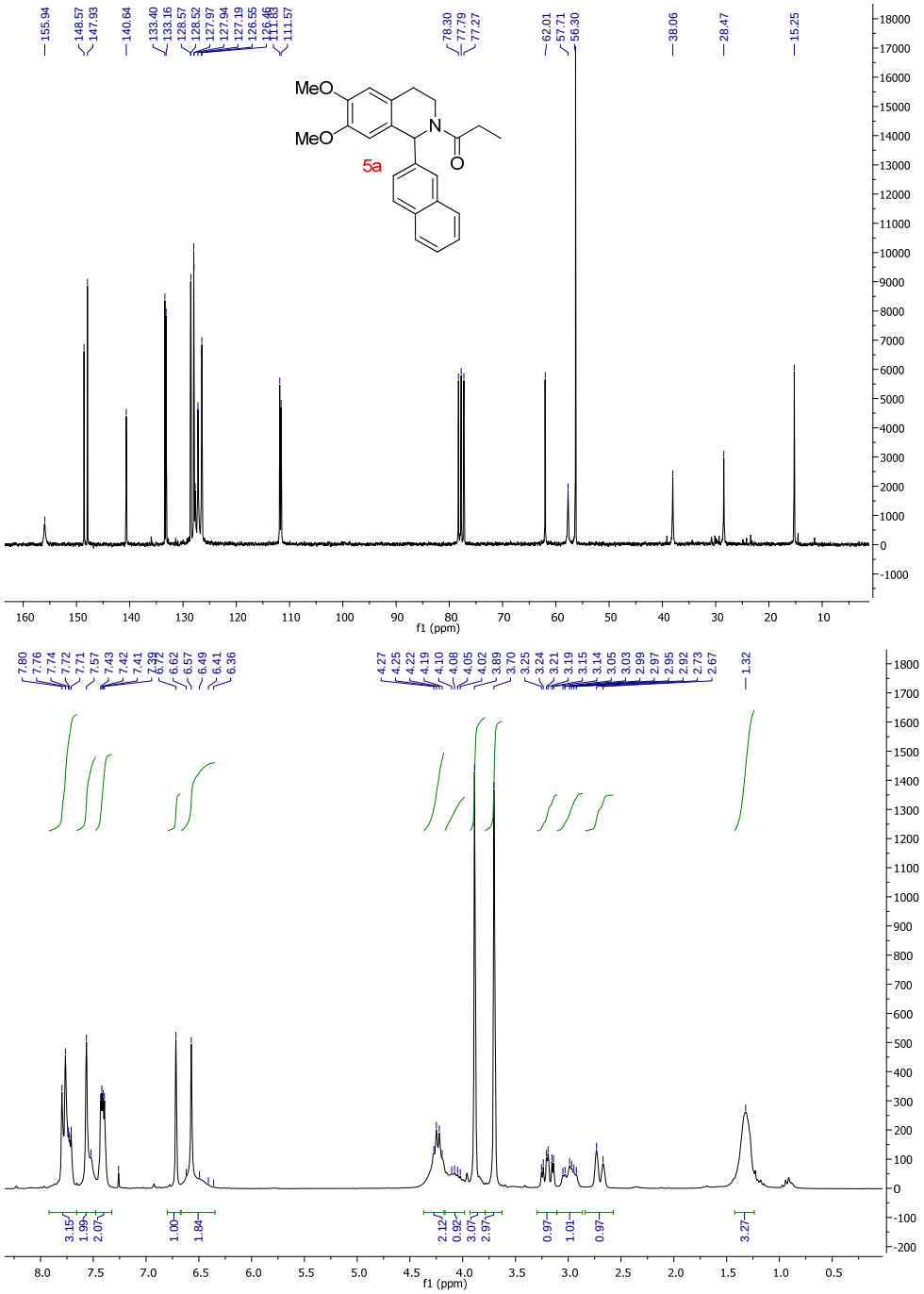
This new method was applied to the synthesis of the pentacyclic saframycin framework. In our first approach, we employed a symmetry-based strategy following the ACE-D-B order for ring formation and achieved the generation of ring B by application of the previously developed α-amidosulfone variation of the Pictet-Spengler reaction. Ring B formation required the presence of a spacer chain at C6 in order to relieve steric compression in the intermediate. The pentacyclic systems obtained in this fashion were initially isolated as mixtures of diastereomers, but the stereochemical outcome of the reaction could be directed to the relative configuration found in the natural products by adjustments in the reaction concentration and by suitable manipulation of the A and E ring substituents. The incorporation of a styryl chain offers, not only a suitable spacer, but also the possibility of oxidative functionalization at C9.

An alternative symmetry-based strategy following the ACE-B-D order for ring formation was also examined, leading to a very concise synthesis of the pentacyclic core of the saframycins. This route is based on the regio and diastereoselective initial generation of ring B using the α-amidosulfone variation of the Pictet-Spengler reaction. The diastereoselectivity of this reaction was governed by the substituent at C6 and the substitution pattern of rings A and E, with the interaction between ring A and the C6 styryl substituent in the α-amidosulfone intermediate being crucial for the reaction to yield the desired relative configuration. Ring D formation required the selective partial reduction of the C1 carbonyl to a hemiaminal and the use of superacids to induce a Mannich-type cyclization.

A SAR study on compounds combining a urea function and a tetrahydroisoquinoline core as antagonists of the TRPM8 protein, which is involved in the intracelular uptake of calcium, led to promising data showing apoptosis induction in cancer cells where this ion cannel is overexpressed. Some tetrahydropyrazinoisoquinolines were also potent

antagonists of this cannel, specially those bearing methoxy groups at R_1 y R_4 in rings A and E.

8. Capítulo VIII. Espectros.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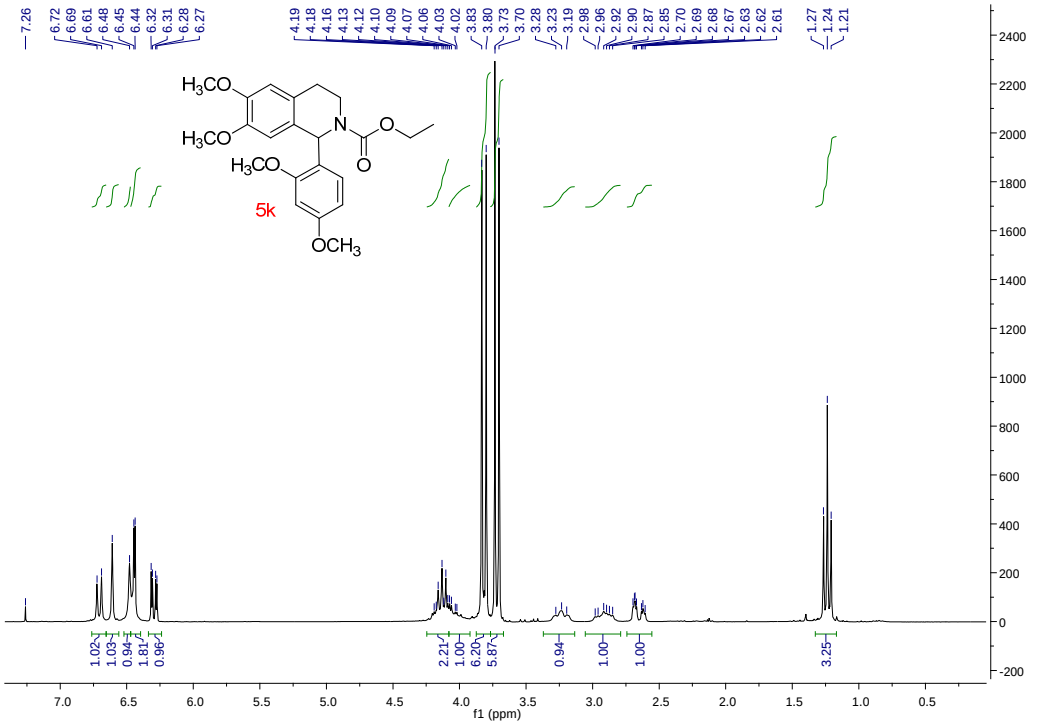
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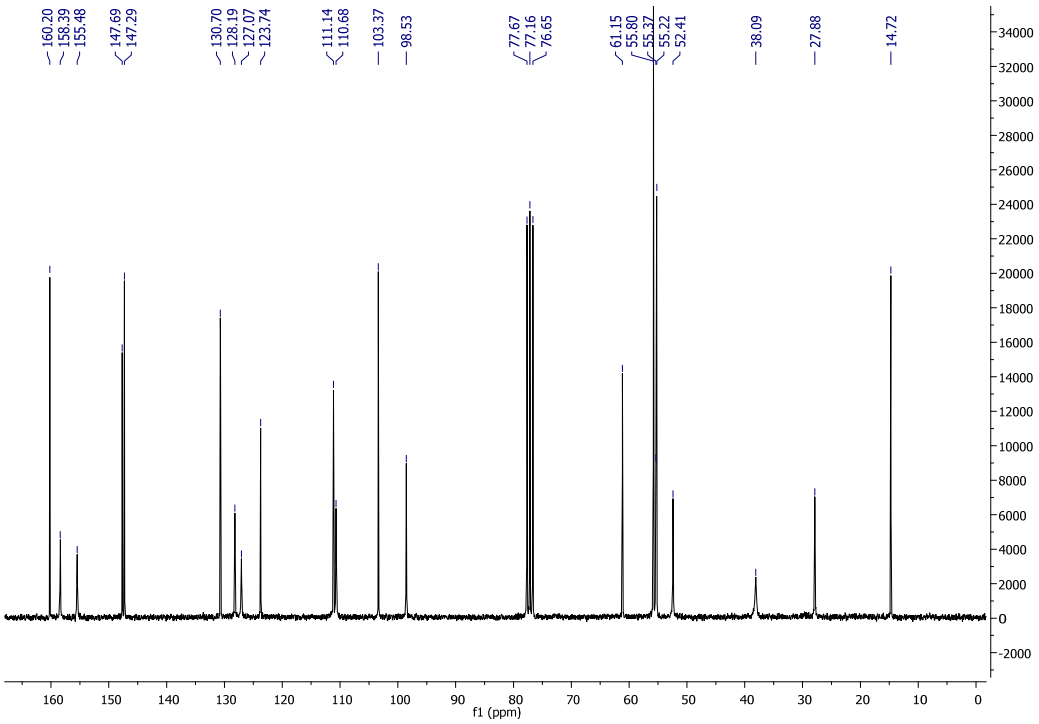
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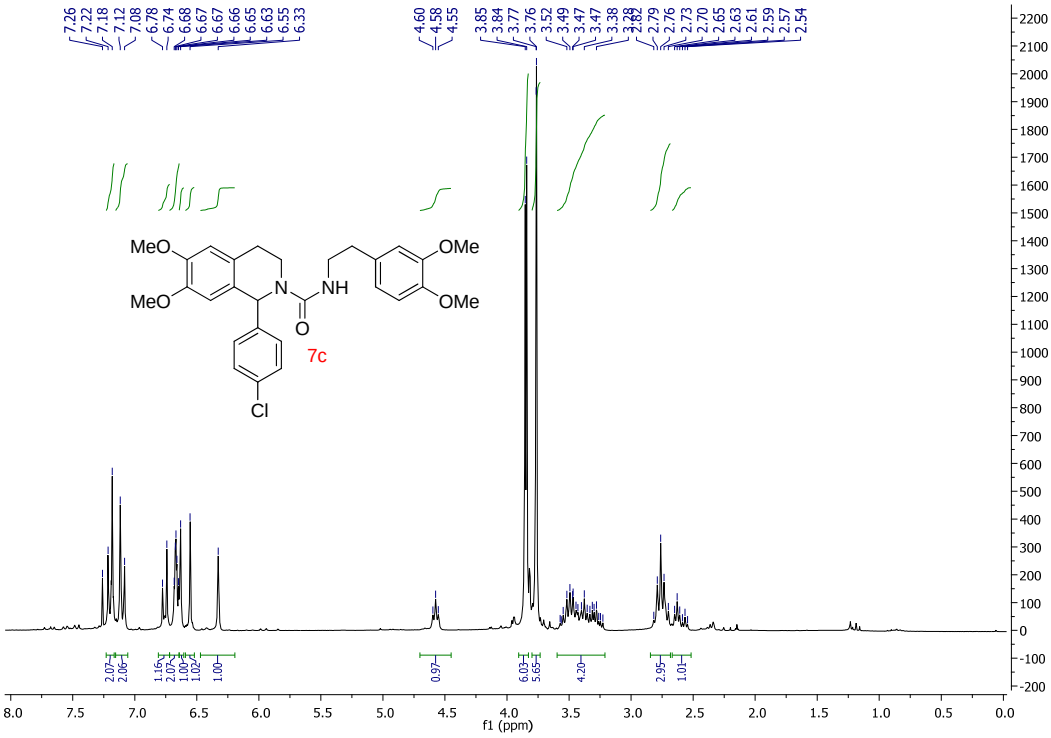
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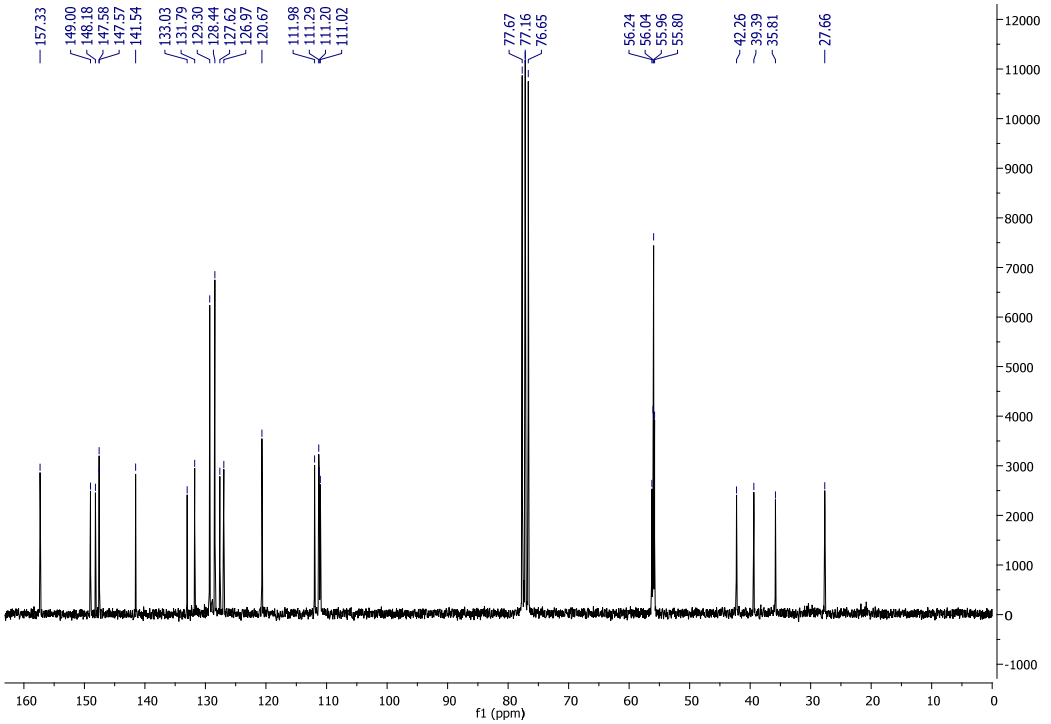
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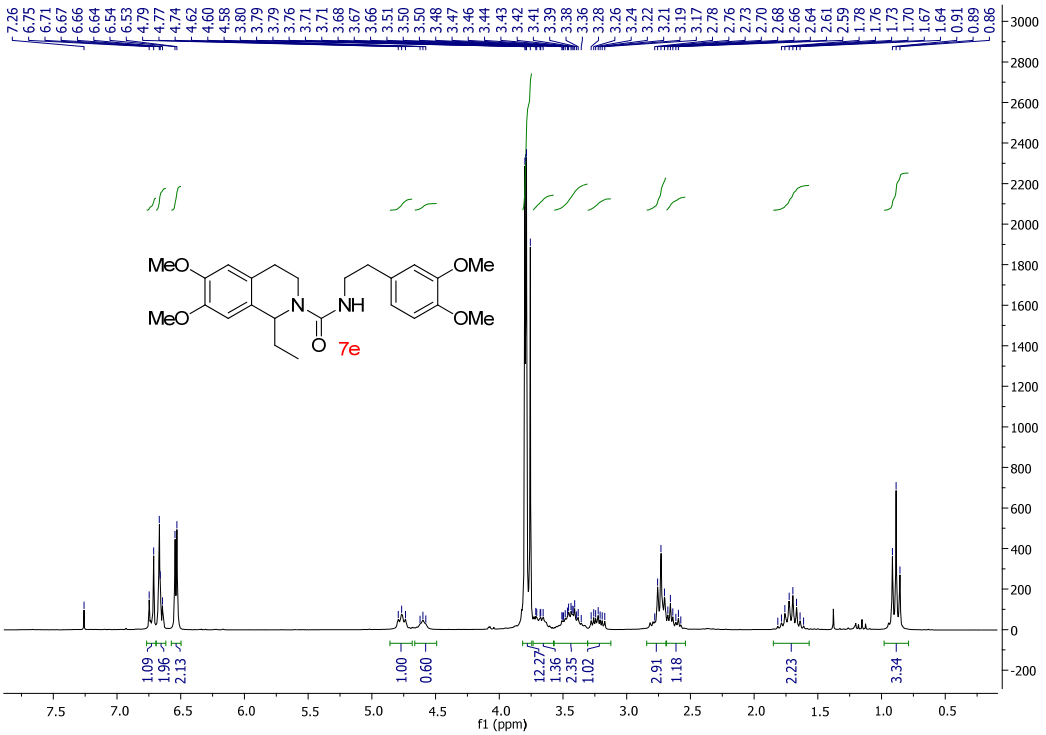
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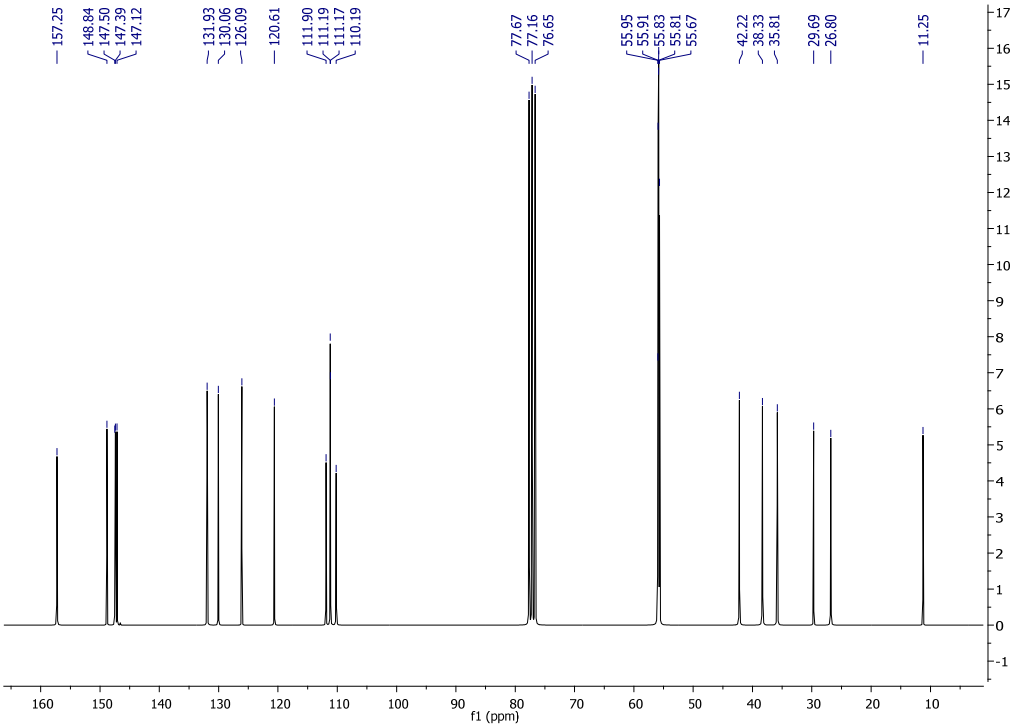
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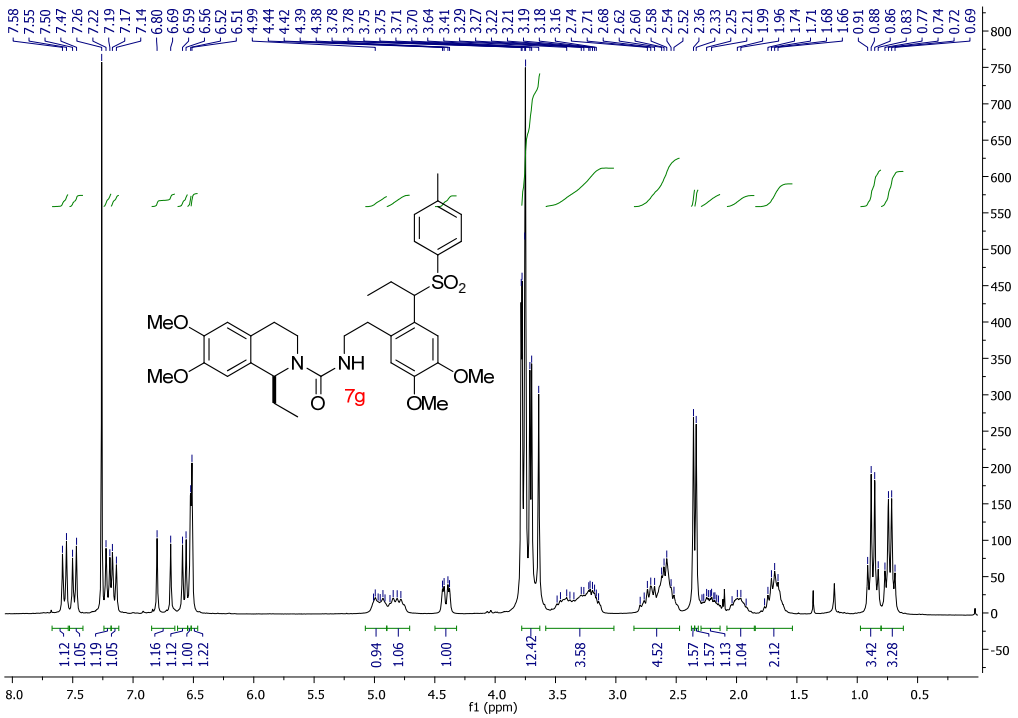
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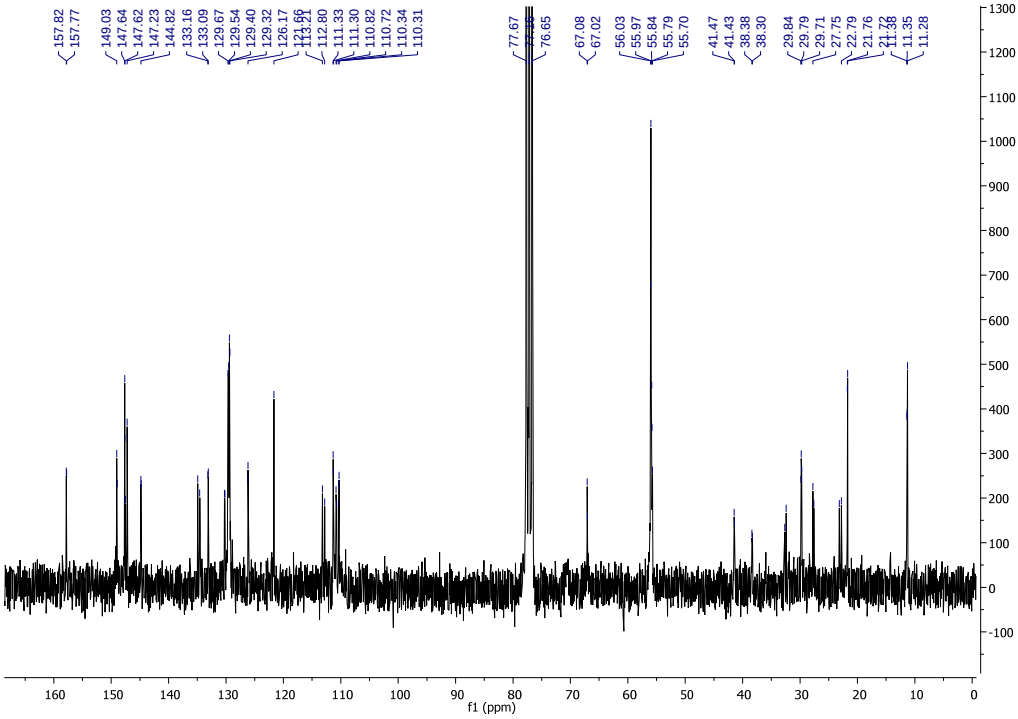
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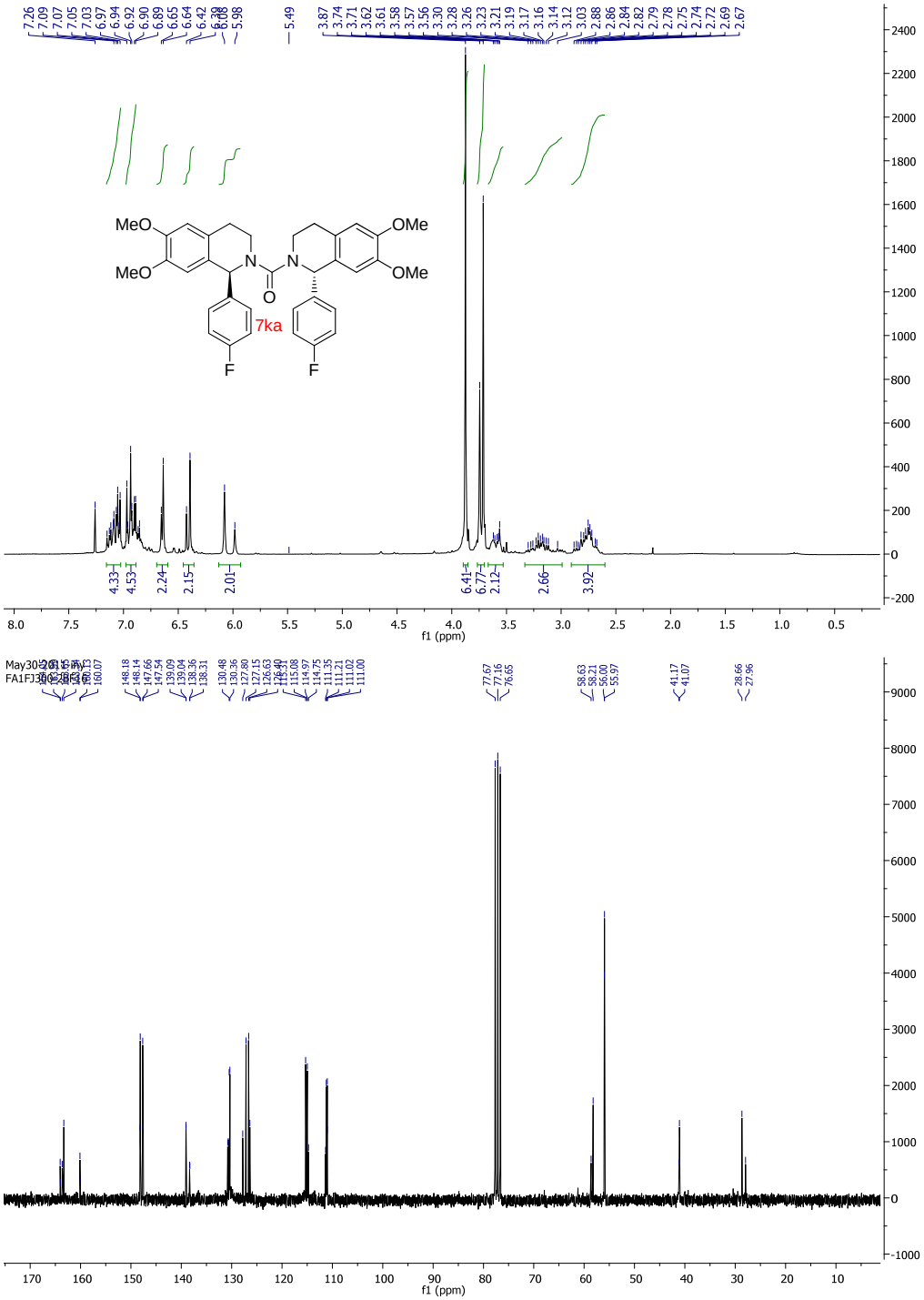
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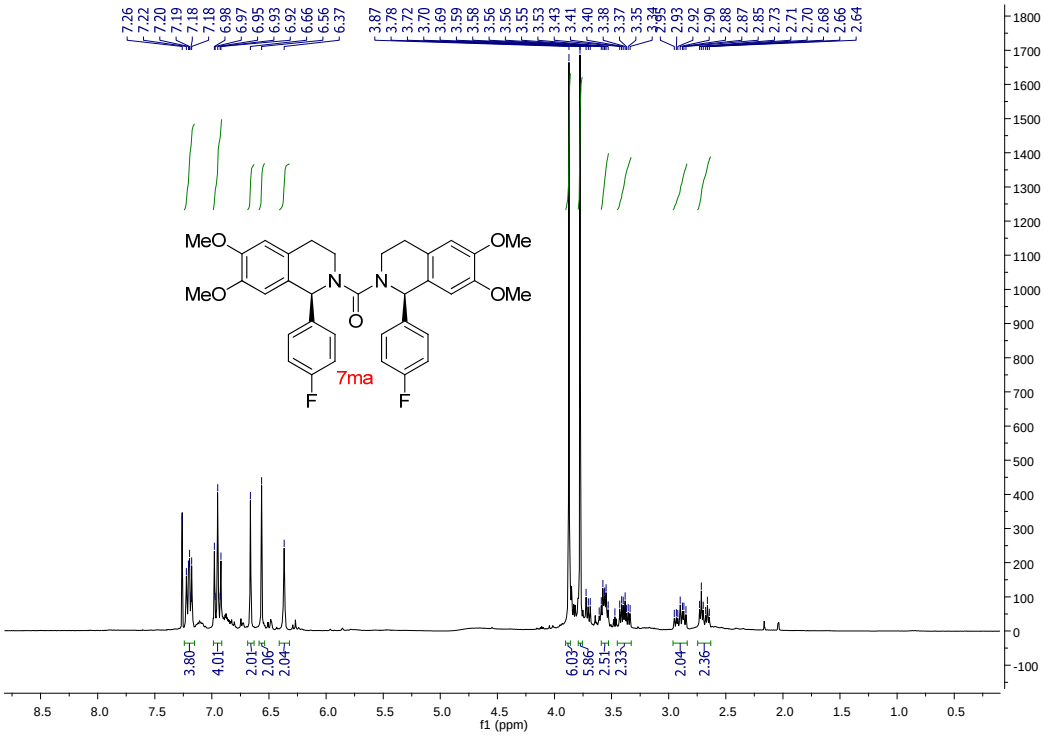
f1 (ppm)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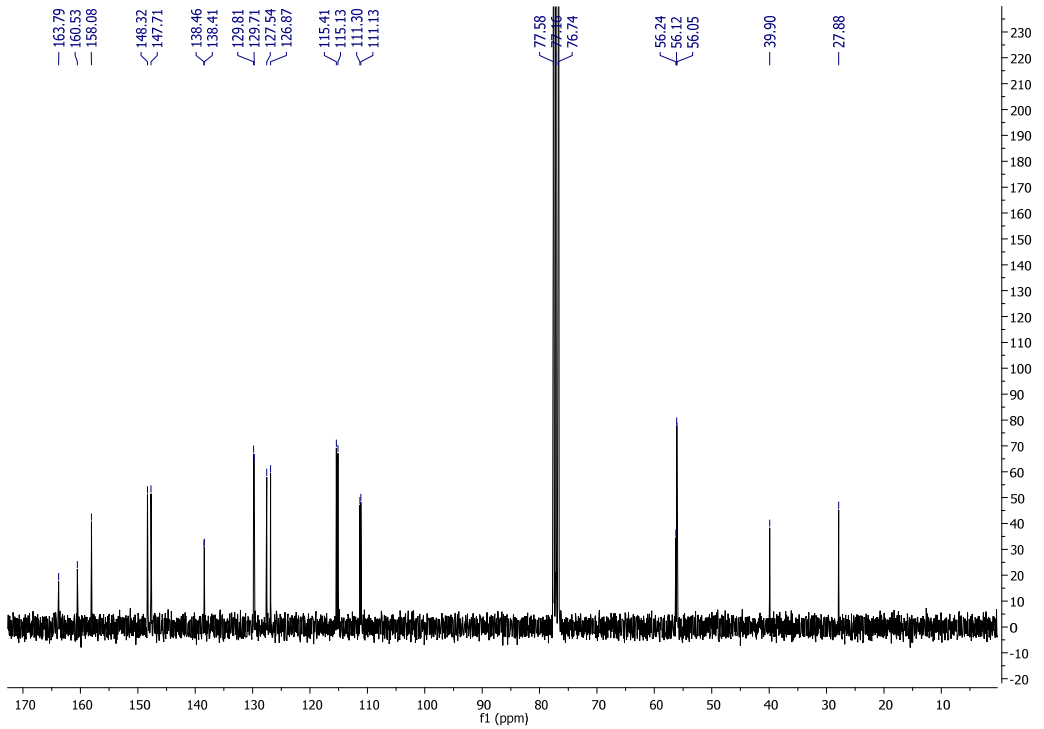
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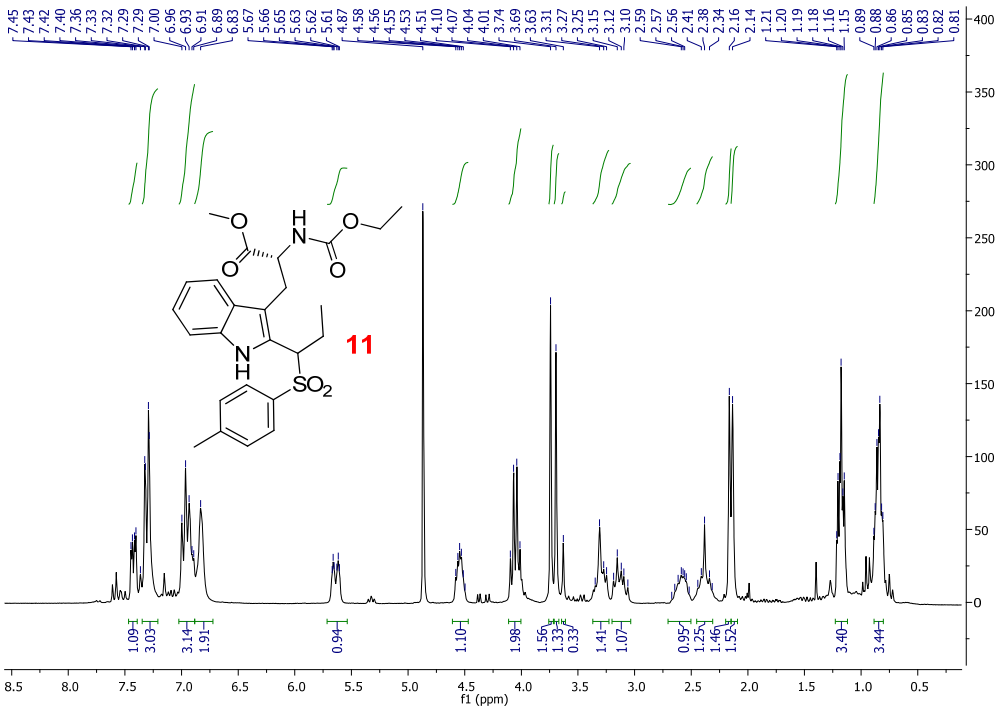
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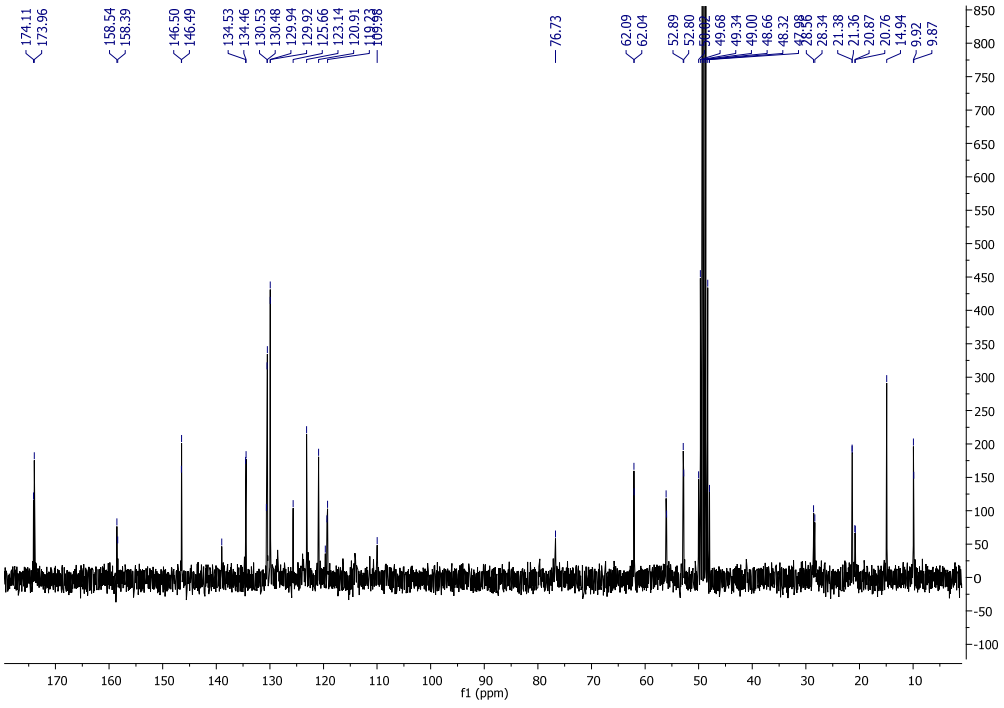
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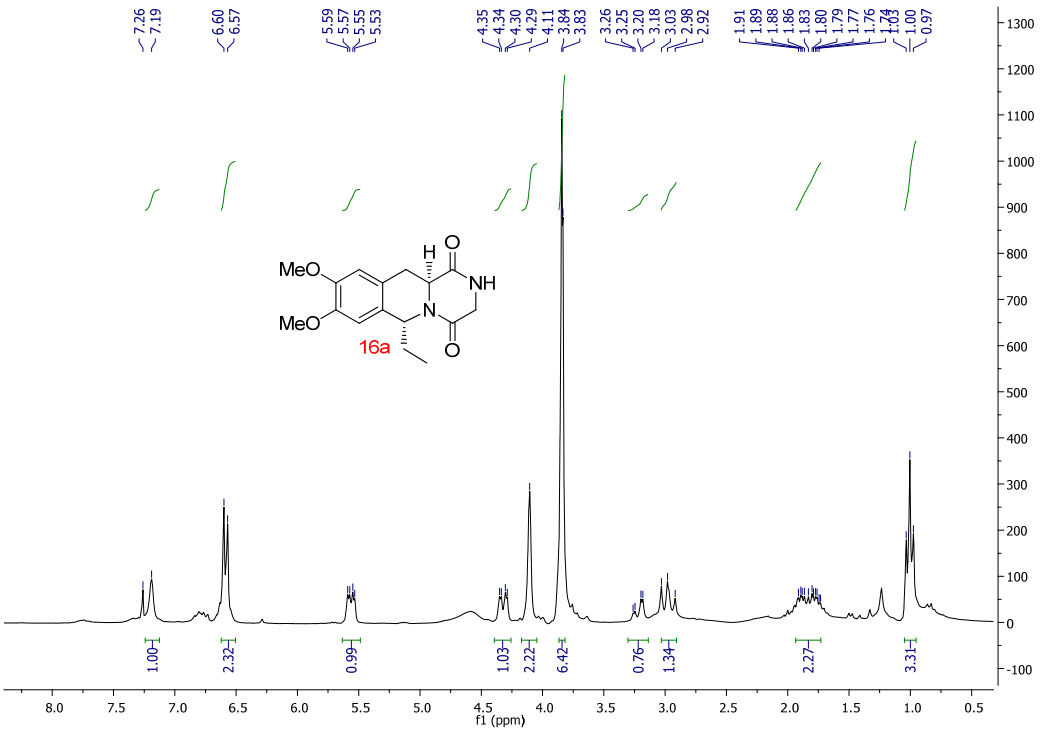
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MeO
H
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NH
N
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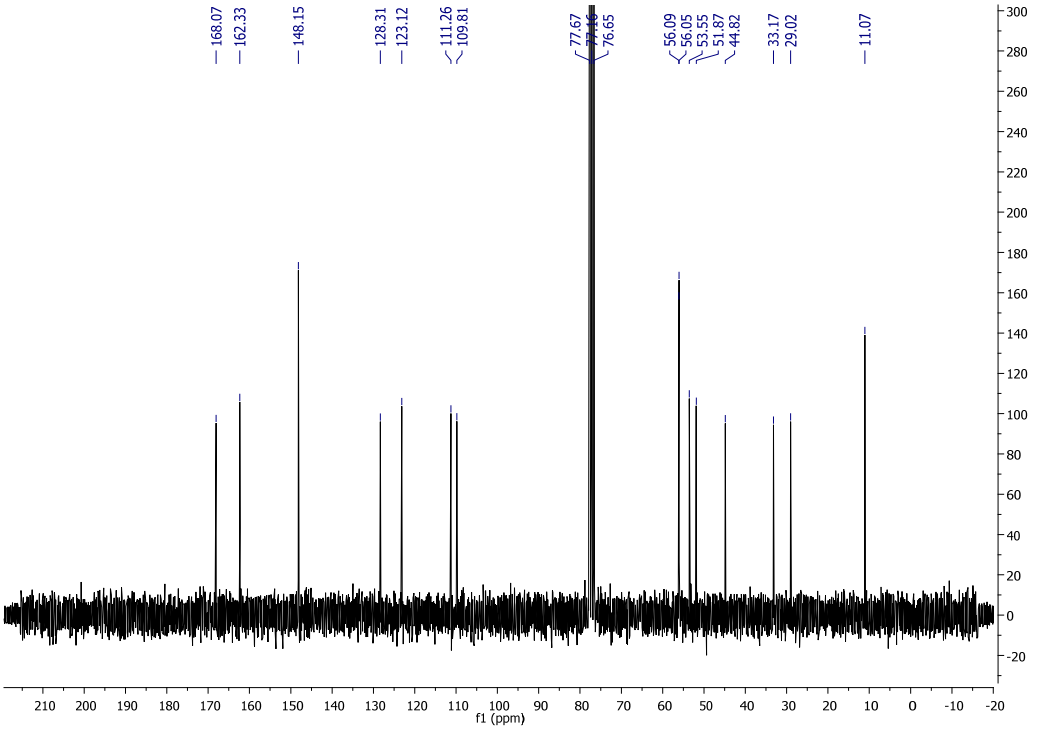
2.27
3.31
f1 (ppm)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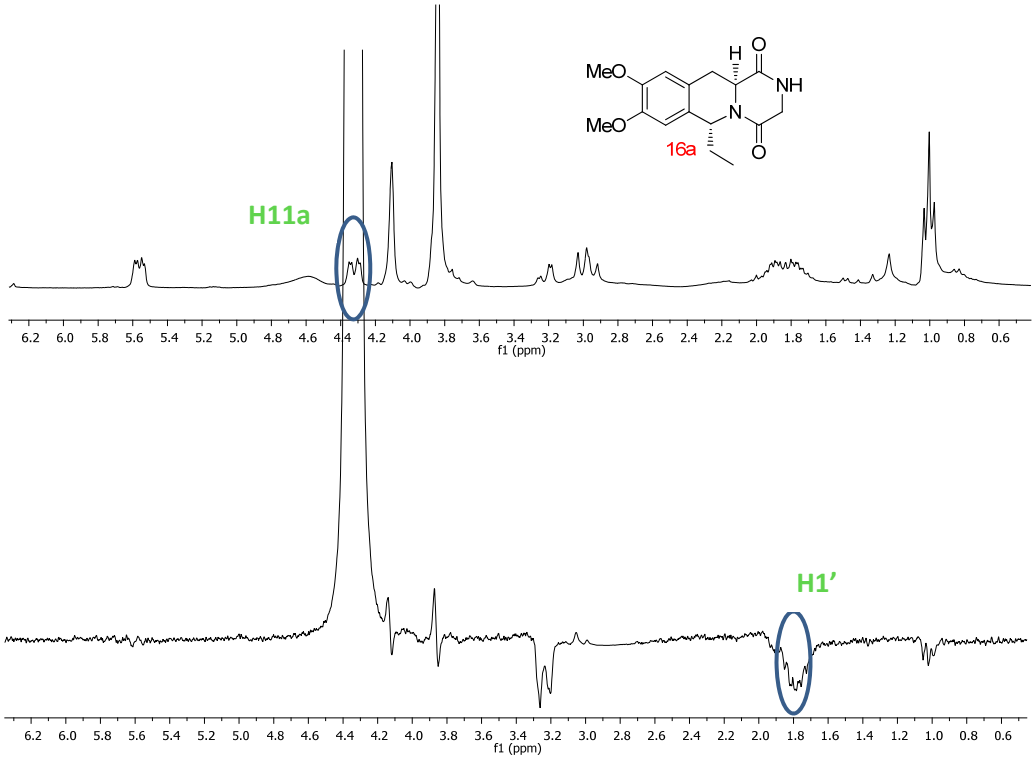
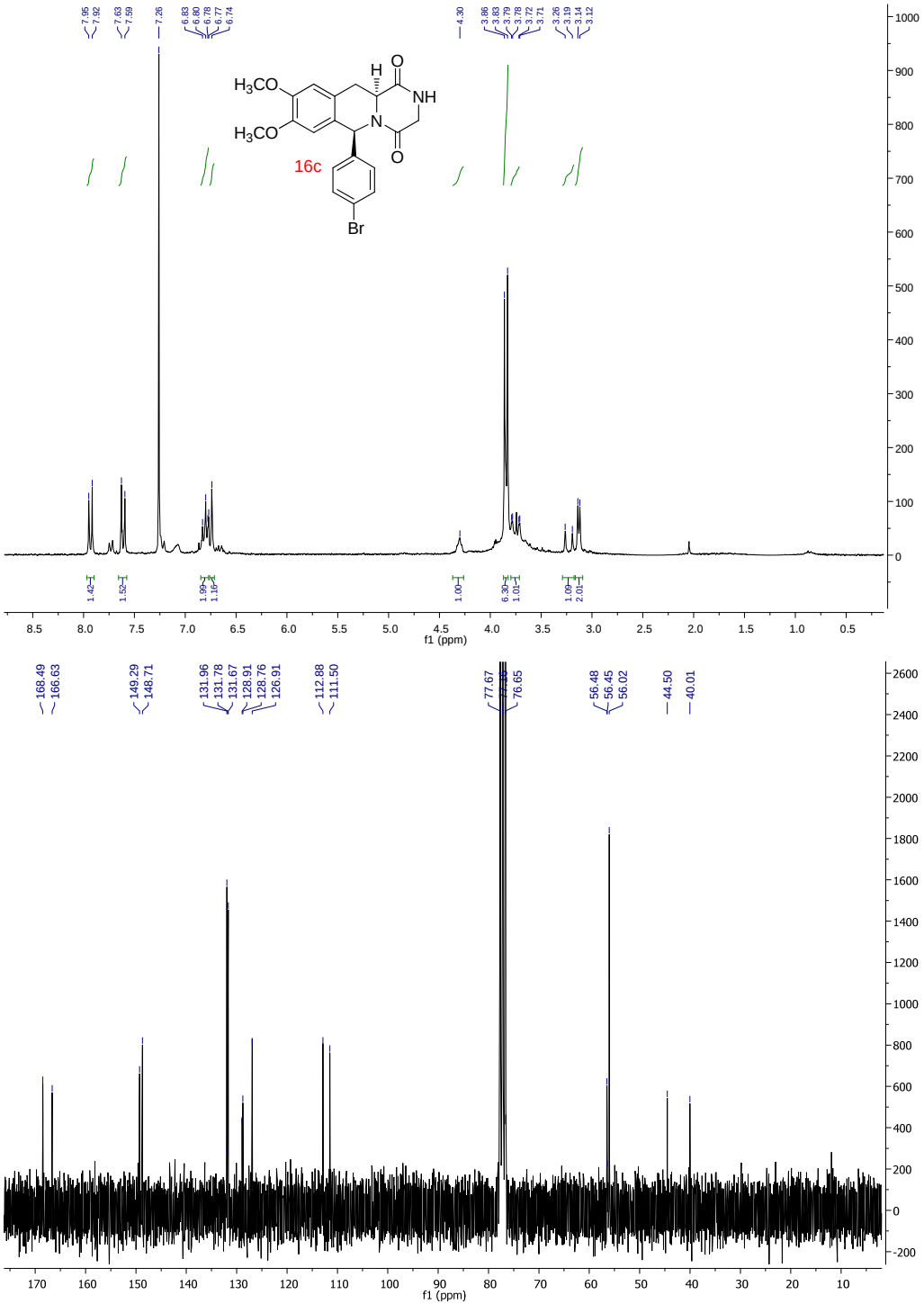
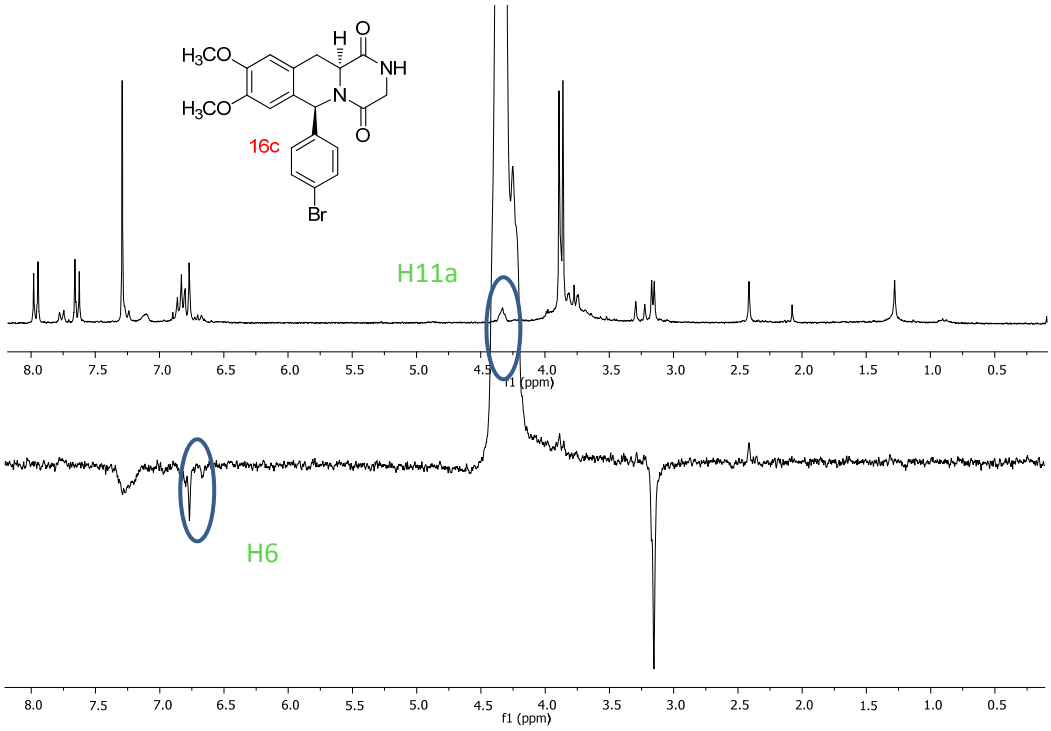
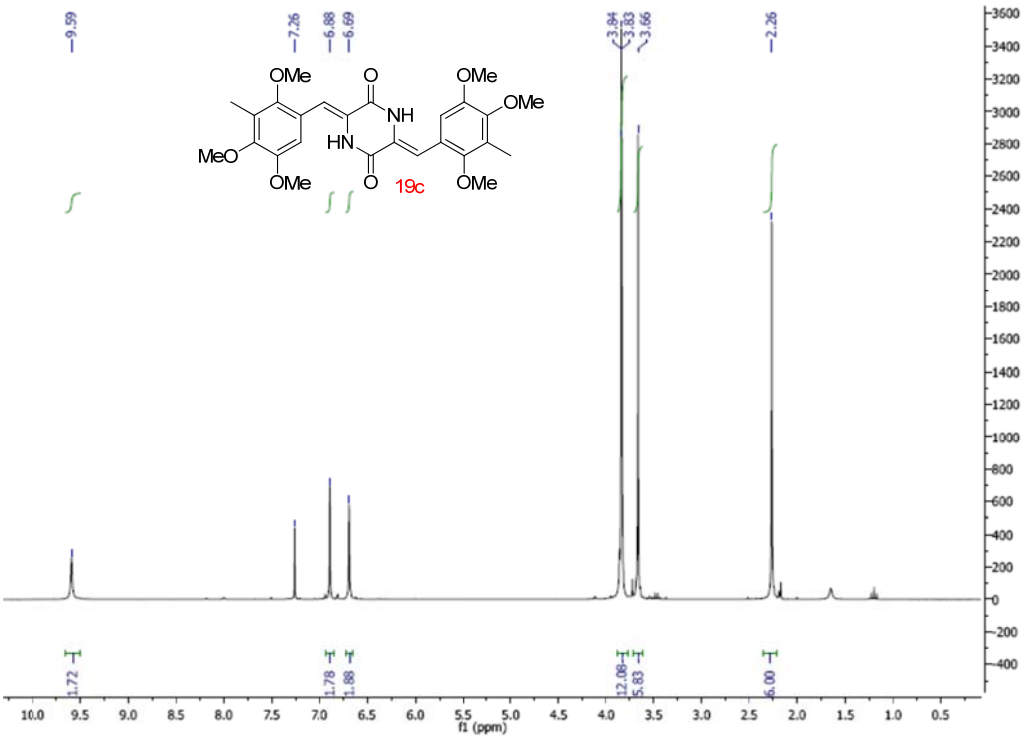
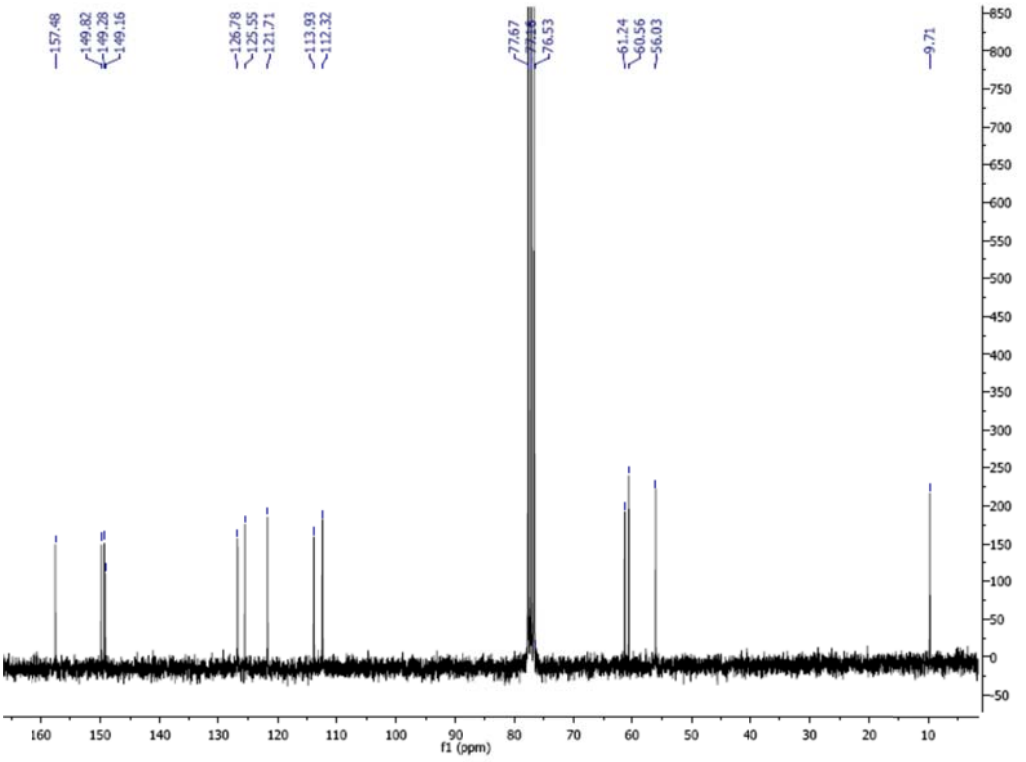
162.33
148.15
128.31
123.12
111.26
109.81
77.67
77.46
76.65
56.09
56.05
53.55
51.87
44.82
33.17
29.02
11.07
f1 (ppm)

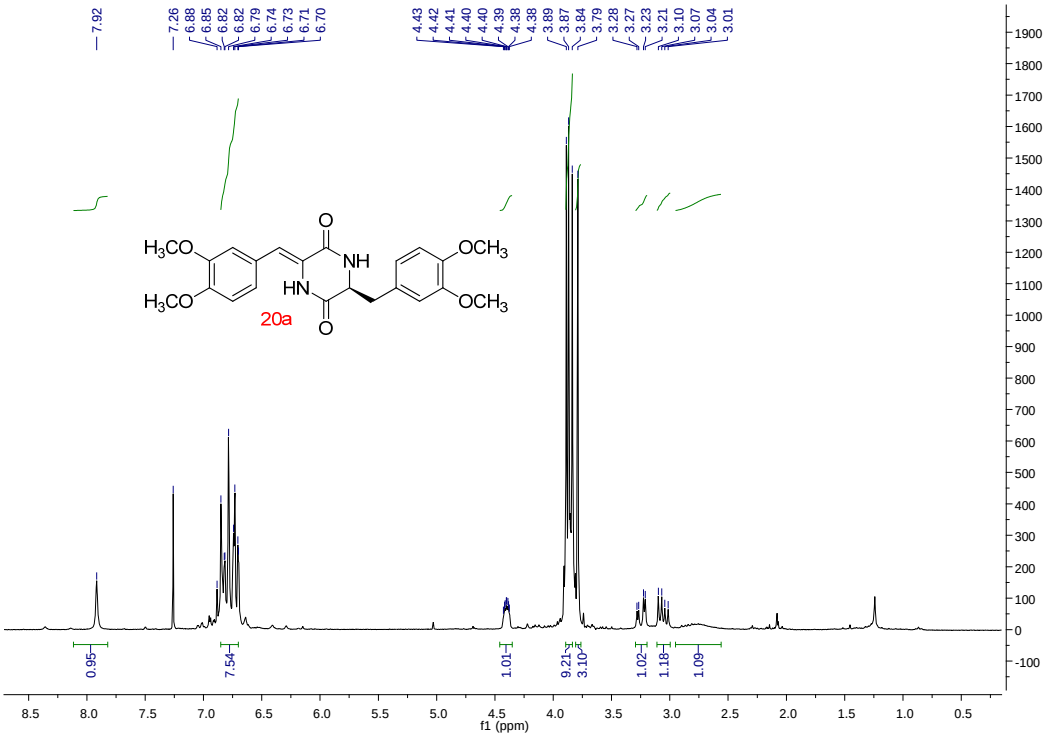

MeO
MeO
H
O
NH
N
O
16a
H11a
6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f1 (ppm)
H1'
6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f1 (ppm)

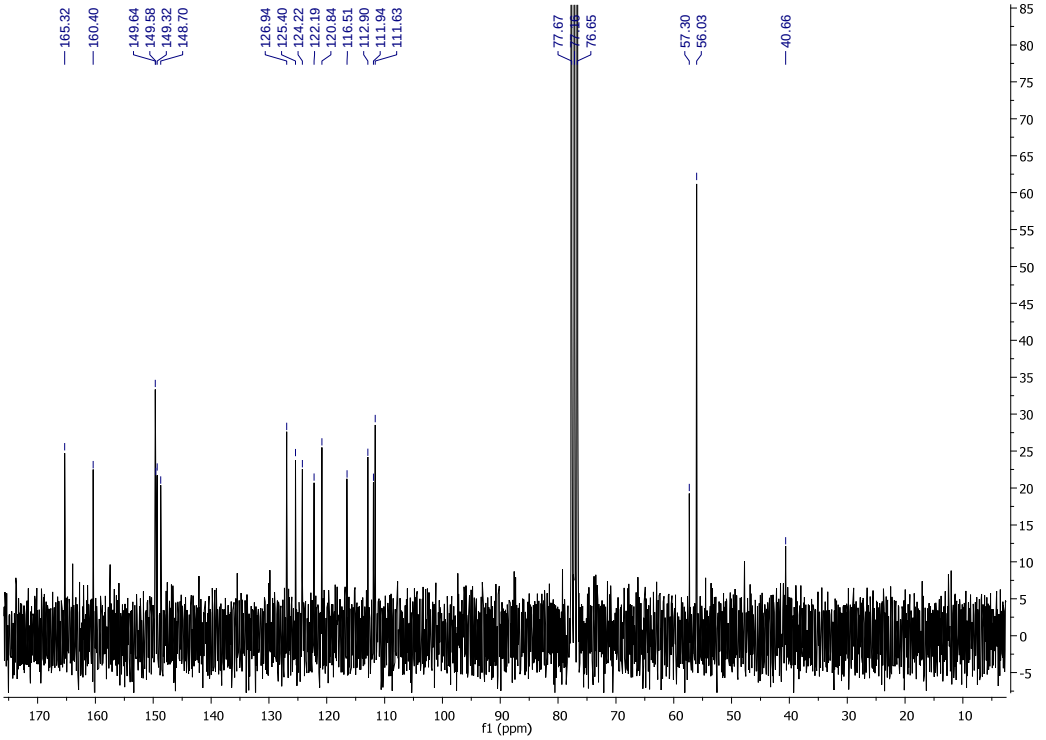

7.95
7.92
7.63
7.59
7.26
6.83
6.80
6.78
6.77
6.74
4.30
3.86
3.83
3.79
3.78
3.72
3.71
3.26
3.19
3.14
3.12
H3CO
H3CO
H
O
NH
N
O
16c
Br
1.42
1.52
1.99
1.16
1.00
6.30
1.01
1.09
2.01
f1 (ppm)
168.49
166.63
149.29
148.71
131.96
131.78
131.67
128.91
128.76
126.91
112.88
111.50
77.67
77.38
76.65
56.48
56.45
56.02
44.50
40.01
f1 (ppm)

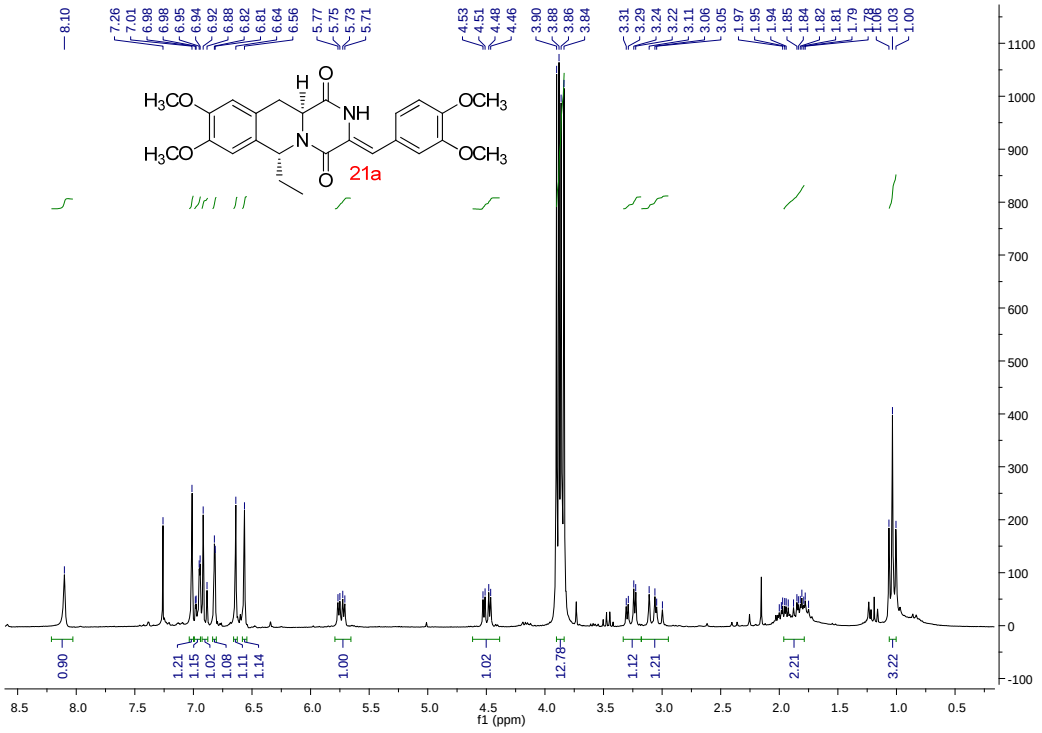

H3CO
H3CO
H
O
NH
N
O
16c
Br
H11a
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
H6
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


9.59
7.26
6.88
6.69
3.84
3.83
3.66
2.26
OMe
O
NH
HN
MeO
OMe
OMe
OMe
O
OMe
19c
1.72
1.78
1.88
12.08
5.83
6.00
f1 (ppm)


157.48
149.82
149.28
149.16
126.78
125.55
121.71
113.93
112.32
77.67
77.16
76.53
61.24
60.56
56.03
9.71
f1 (ppm)


7.92
7.26
6.88
6.85
6.82
6.82
6.79
6.74
6.73
6.71
6.70
4.43
4.42
4.41
4.40
4.40
4.39
4.38
4.38
3.89
3.87
3.84
3.79
3.28
3.27
3.23
3.21
3.10
3.07
3.04
3.01
H3CO
H3CO
NH
HN
O
O
OCH3
OCH3
20a
0.95
7.54
1.01
9.21
3.10
1.02
1.18
1.09
f1 (ppm)


165.32
160.40
149.64
149.58
149.32
148.70
126.94
125.40
124.22
122.19
120.84
116.51
112.90
111.94
111.63
77.67
77.16
76.65
57.30
56.03
40.66
f1 (ppm)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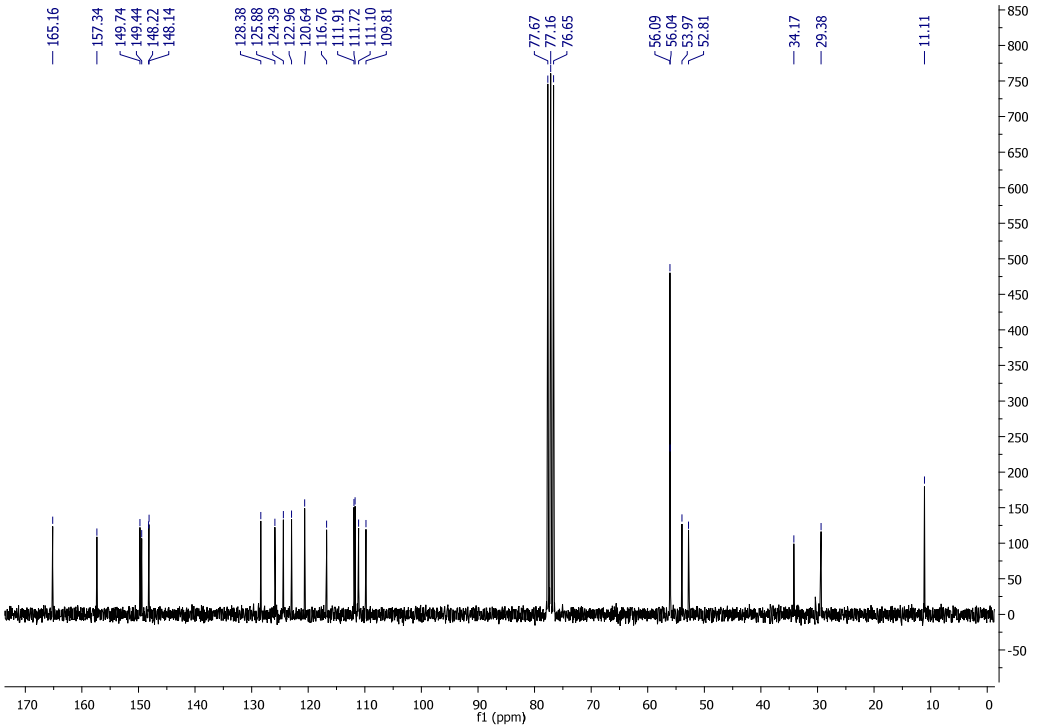
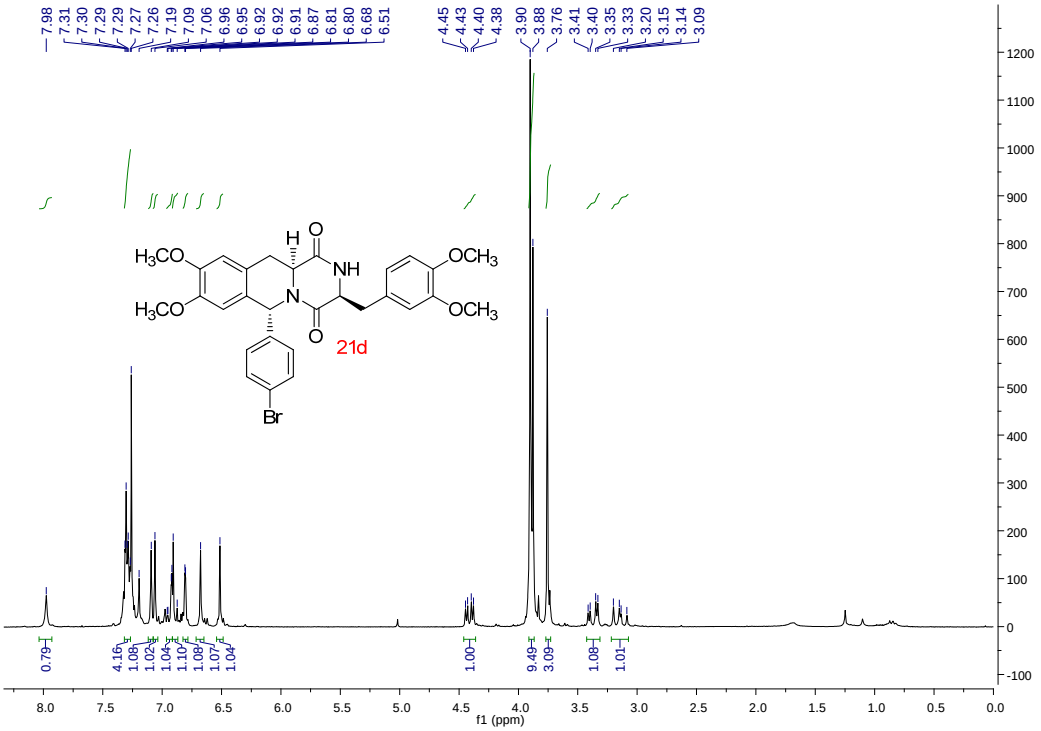
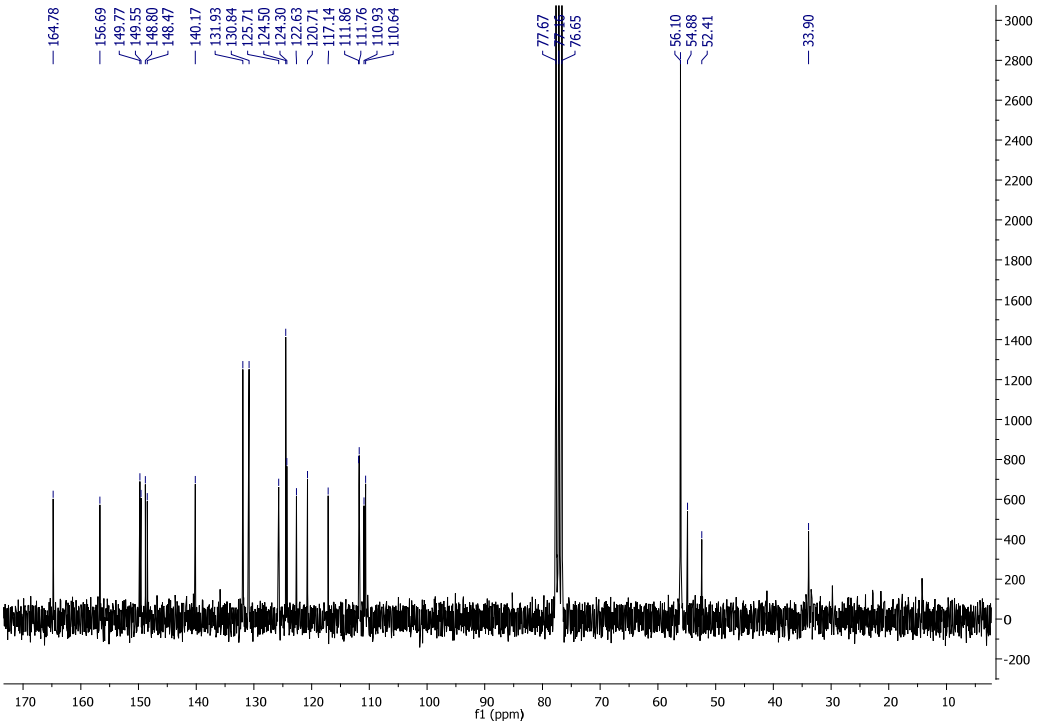
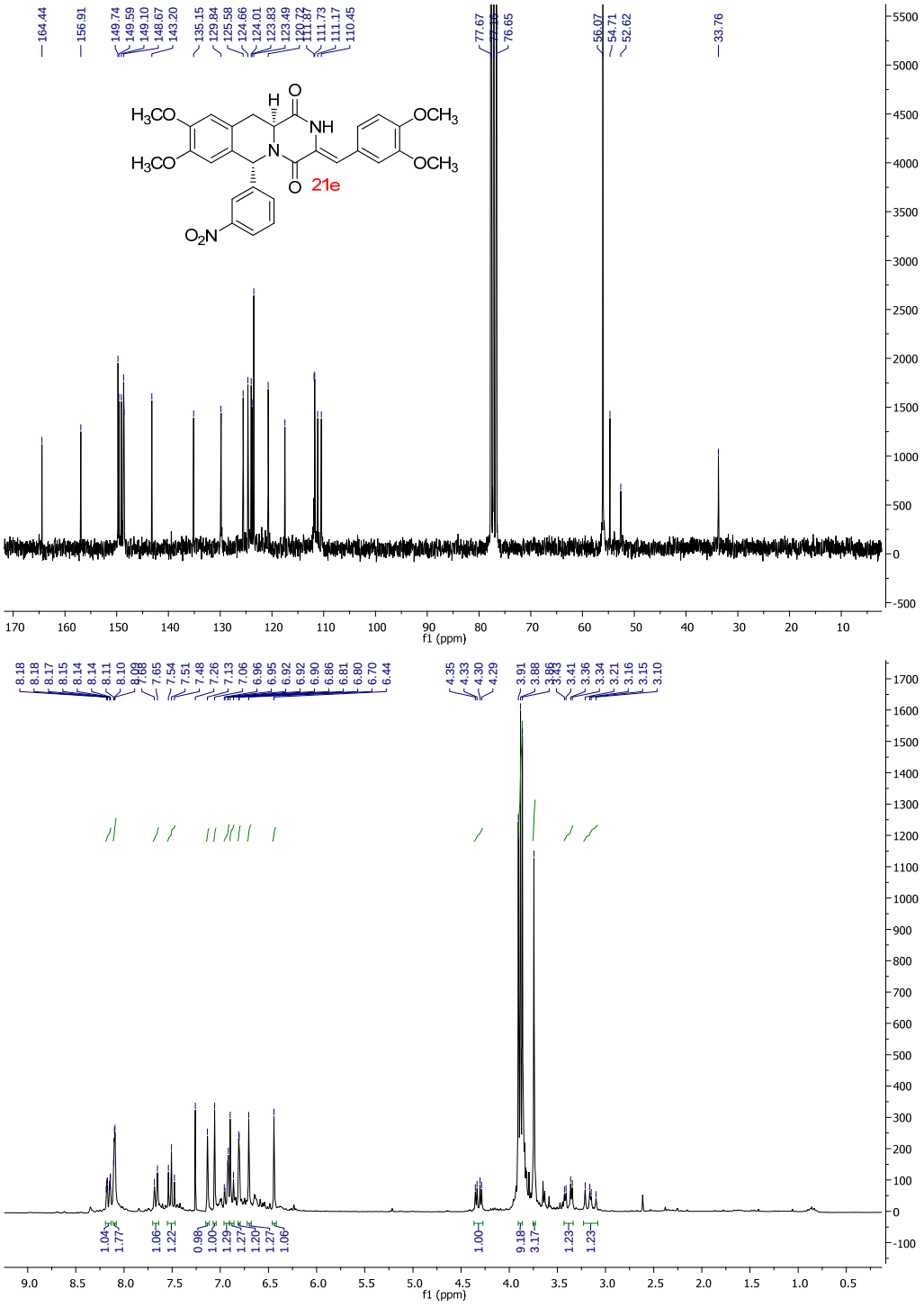
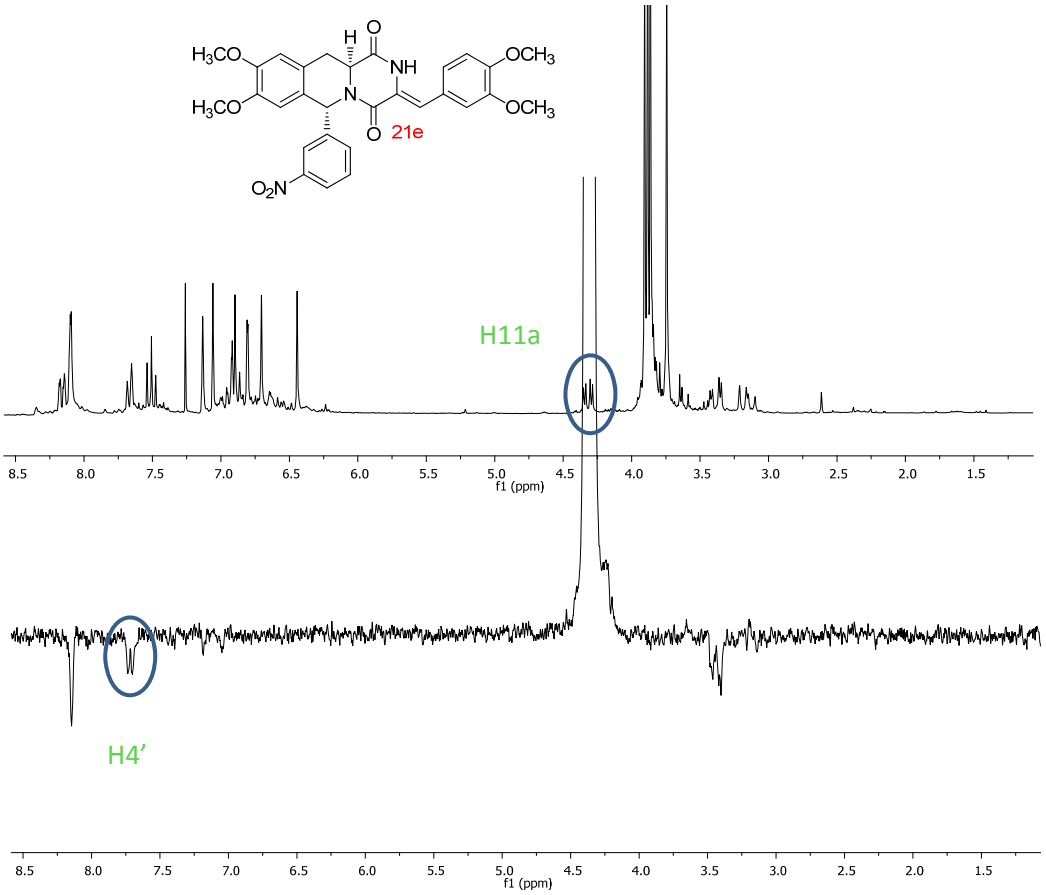
7.26
7.01
6.98
6.98
6.95
6.94
6.92
6.88
6.82
6.81
6.64
6.56
5.77
5.75
5.73
5.71
4.53
4.51
4.48
4.46
3.90
3.88
3.86
3.84
3.31
3.29
3.24
3.22
3.11
3.06
3.05
1.97
1.95
1.94
1.85
1.84
1.82
1.81
1.79
1.78
1.08
1.03
1.00
H
O
NH
N
O
H3CO
H3CO
OCH3
OCH3
21a
0.90
1.21
1.15
1.02
1.08
1.11
1.14
1.00
1.02
12.78
1.12
1.21
2.21
3.22
f1 (ppm)

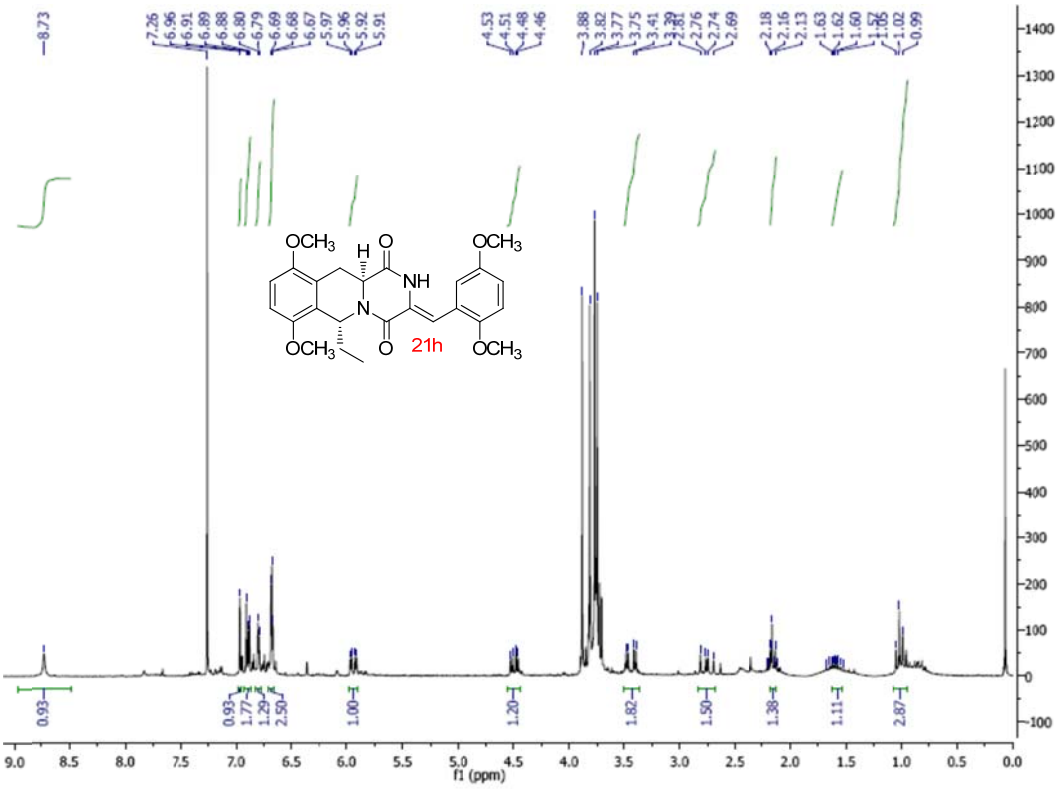

165.16
157.34
149.74
149.44
148.22
148.14
128.38
125.88
124.39
122.96
120.64
116.76
111.91
111.72
111.10
109.81
77.67
77.16
76.65
56.09
56.04
53.97
52.81
34.17
29.38
11.11
f1 (ppm)

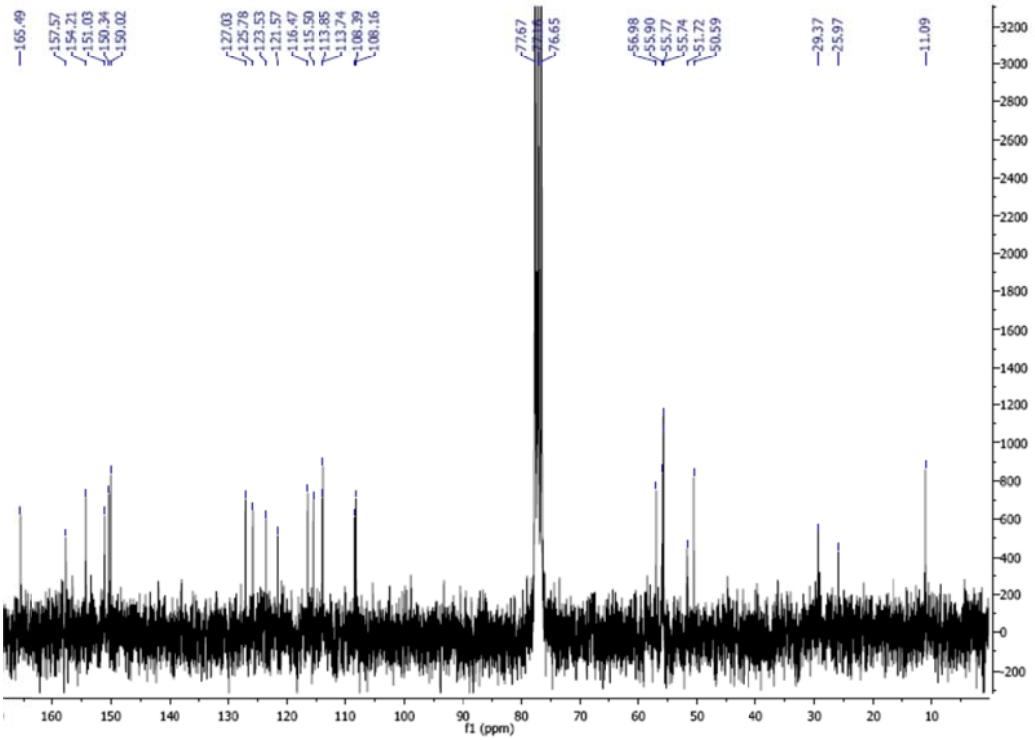

7.98
7.31
7.30
7.29
7.29
7.27
7.26
7.19
7.09
7.06
6.96
6.95
6.92
6.92
6.91
6.87
6.81
6.80
6.68
6.51
4.45
4.43
4.40
4.38
3.90
3.88
3.76
3.41
3.40
3.35
3.33
3.20
3.15
3.14
3.09
H
O
NH
N
O
H3CO
H3CO
OCH3
OCH3
Br
21d
0.79
4.16
1.08
1.02
1.04
1.10
1.08
1.07
1.04
1.00
9.49
3.09
1.08
1.01
f1 (ppm)

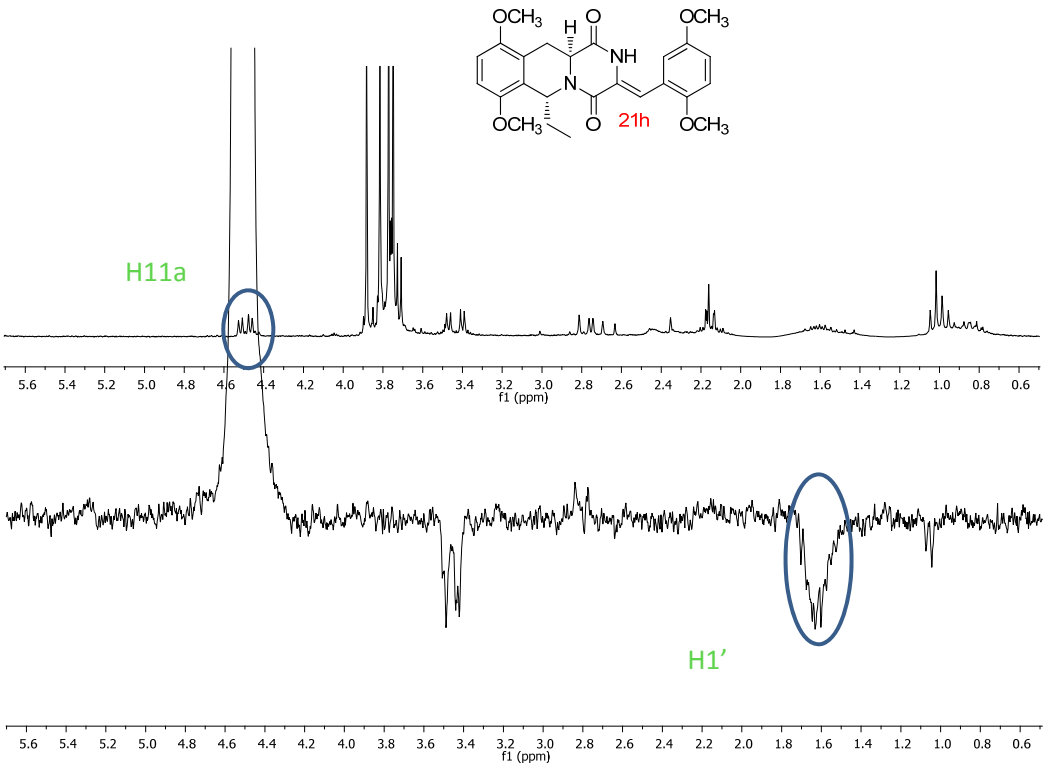

164.78
156.69
149.77
149.55
148.80
148.47
140.17
131.93
130.84
125.71
124.50
124.30
122.63
120.71
117.14
111.86
111.76
110.93
110.64
77.67
77.16
76.65
56.10
54.88
52.41
33.90
f1 (ppm)

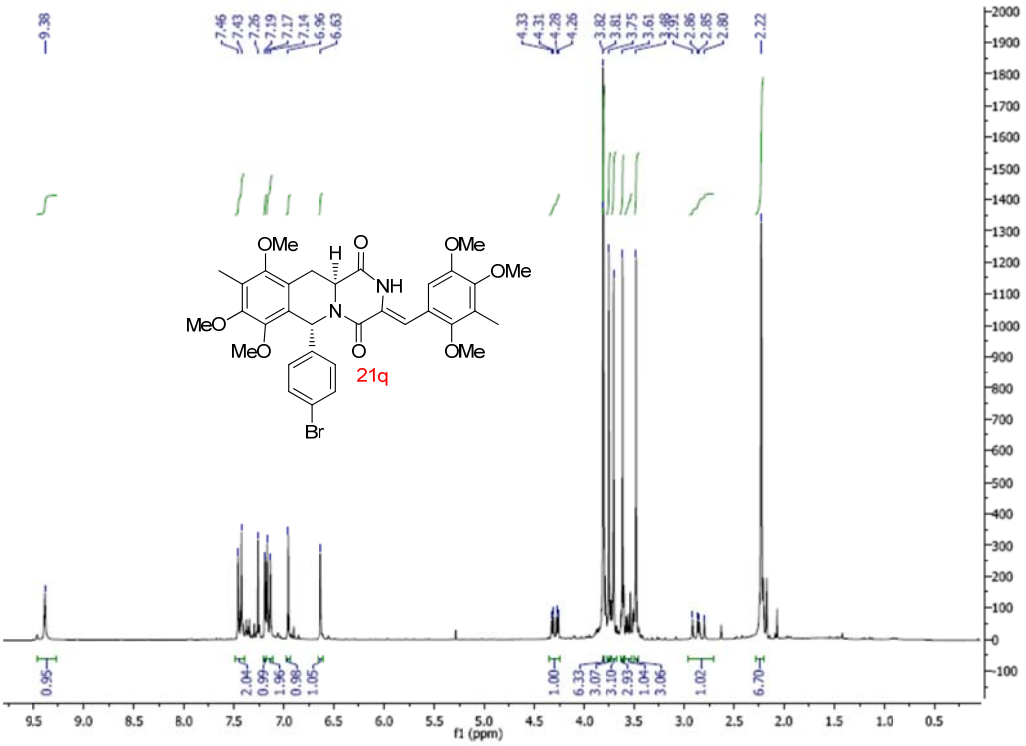

164.44
156.91
149.74
149.59
149.10
148.67
143.20
135.15
129.84
125.58
124.66
124.01
123.83
123.49
111.73
111.17
110.45
77.67
76.65
56.07
54.71
52.62
33.76
H3CO
H3CO
OCH3
OCH3
NH
N
O
21e
O2N
f1 (ppm)
8.18
8.17
8.15
8.14
8.11
8.10
7.65
7.54
7.51
7.48
7.26
7.13
7.06
6.96
6.95
6.92
6.90
6.86
6.81
6.80
6.70
6.44
4.35
4.33
4.30
4.29
3.91
3.88
3.41
3.36
3.34
3.21
3.16
3.15
3.10
1.04
1.77
1.06
1.22
0.98
1.00
1.29
1.27
1.20
1.27
1.06
1.00
9.18
3.17
1.23
1.23
f1 (ppm)

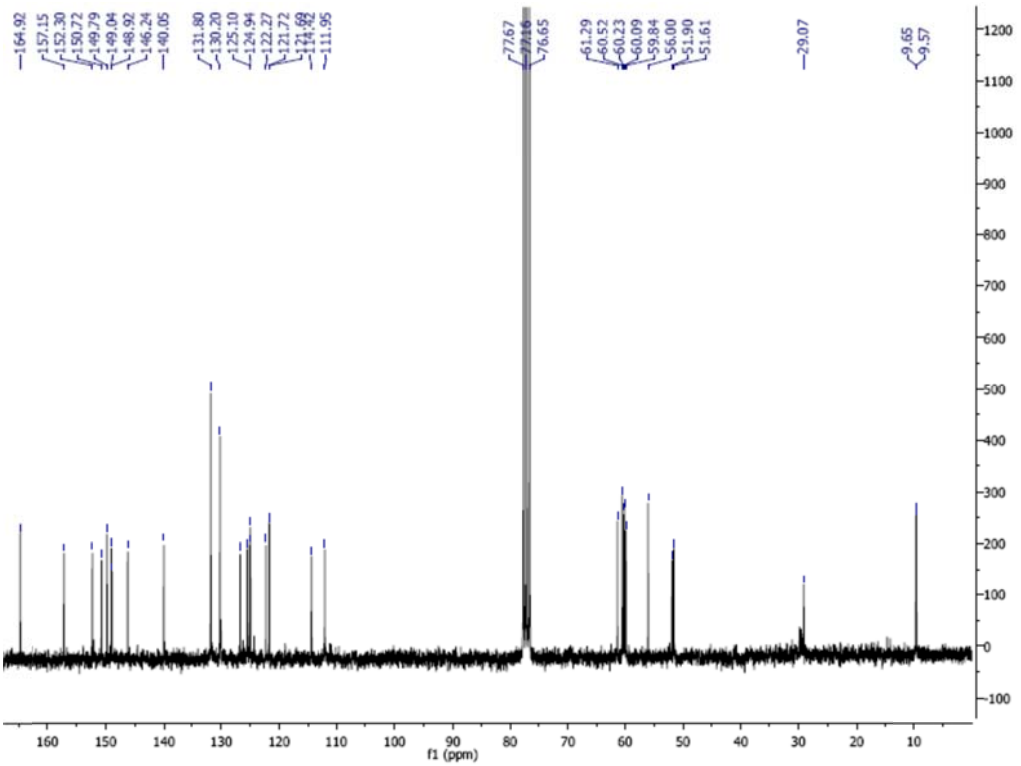

H3CO
H3CO
H
O
NH
N
O
OCH3
OCH3
O2N
21e
H11a
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)
H4'
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

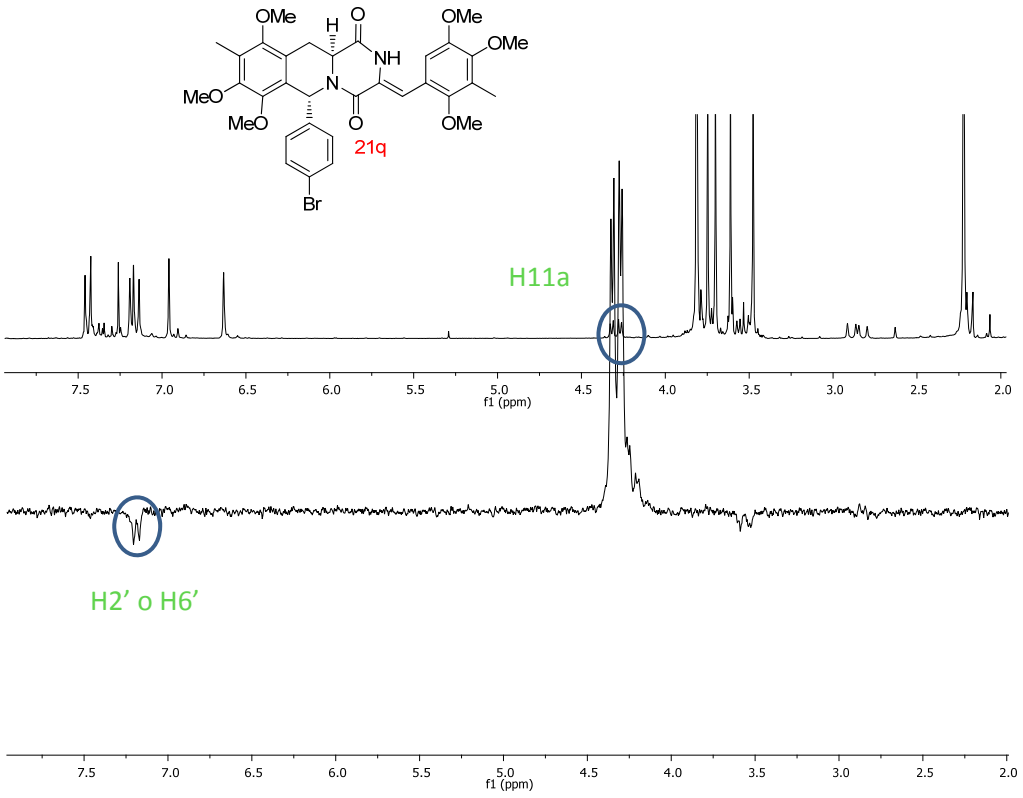

OCH3
H
O
NH
N
O
OCH3
OCH3
OCH3
O
21h
f1 (ppm)

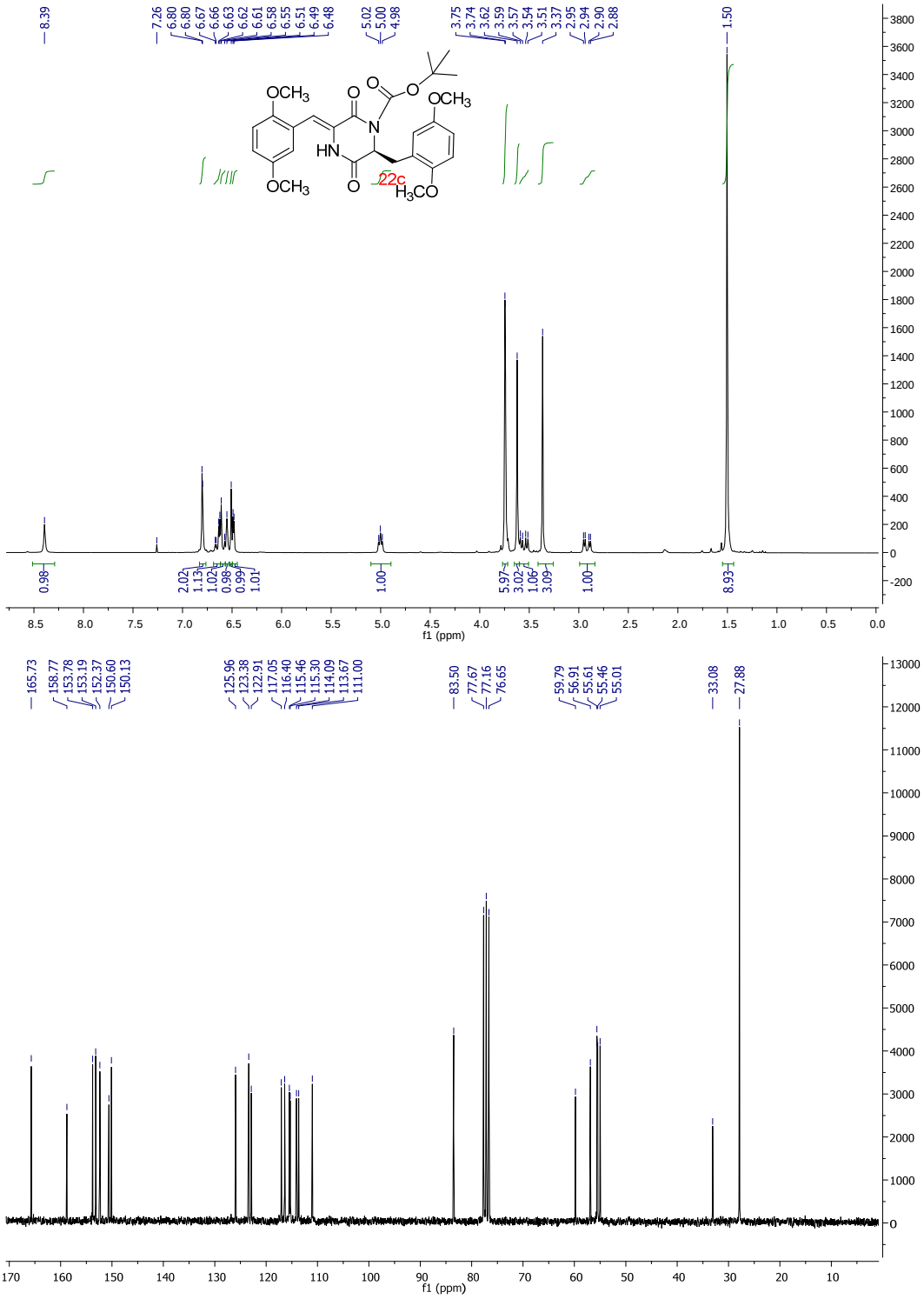

f1 (ppm)

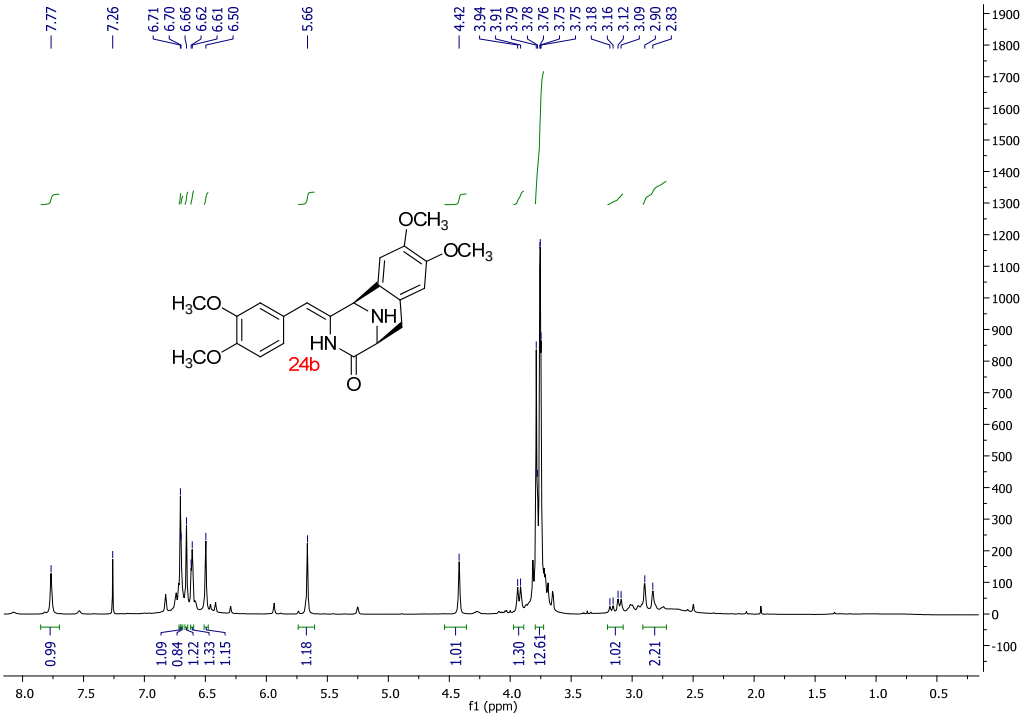

OCH3
H
O
OCH3
NH
N
OCH3
O
21h
OCH3
H11a
5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f1 (ppm)
H1'
5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f1 (ppm)


OMe
H
O
OMe
OMe
NH
MeO
N
MeO
O
OMe
21q
Br
f1 (ppm)


f1 (ppm)


OMe
H
O
OMe
OMe
NH
N
MeO
MeO
O
OMe
21q
Br
H11a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)
H2’ o H6’


8.39
7.26
6.80
6.80
6.67
6.66
6.63
6.62
6.61
6.58
6.55
6.51
6.49
6.48
5.02
5.00
4.98
3.75
3.74
3.62
3.59
3.57
3.54
3.51
3.37
2.95
2.94
2.90
2.88
1.50
OCH3
OCH3
OCH3
H3CO
HN
N
O
22c
0.98
2.02
1.13
1.02
0.98
0.99
1.01
1.00
5.97
3.02
1.06
3.09
1.00
8.93
f1 (ppm)
165.73
158.77
153.78
153.19
152.37
150.60
150.13
125.96
123.38
122.91
117.05
116.40
115.46
115.30
114.09
113.67
111.00
83.50
77.67
77.16
76.65
59.79
56.91
55.61
55.46
55.01
33.08
27.88
f1 (ppm)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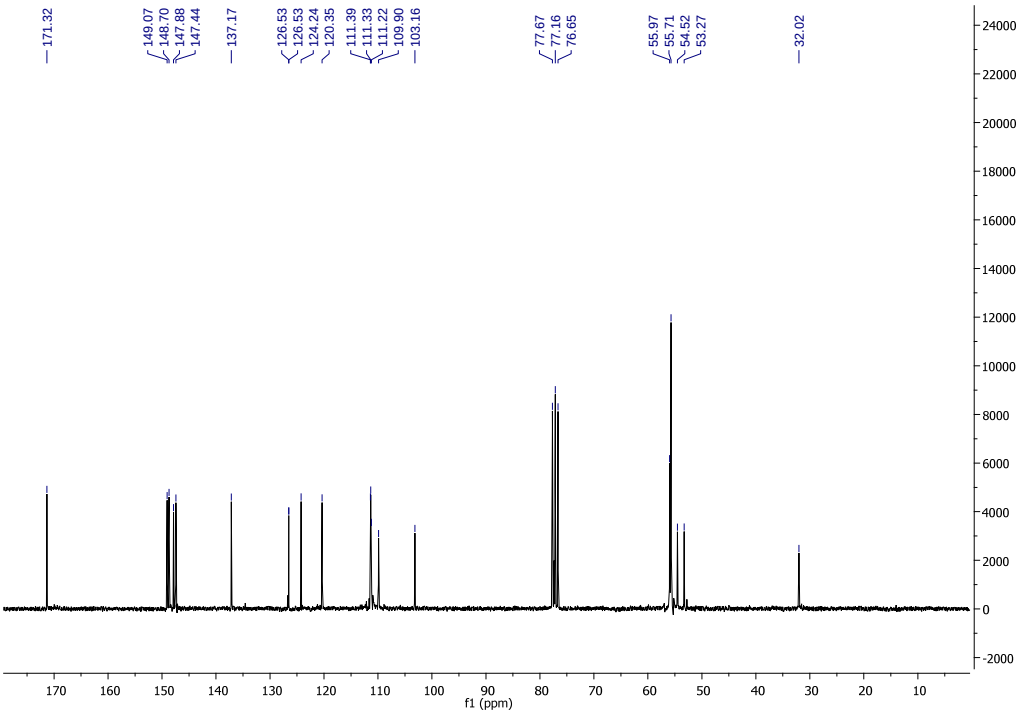
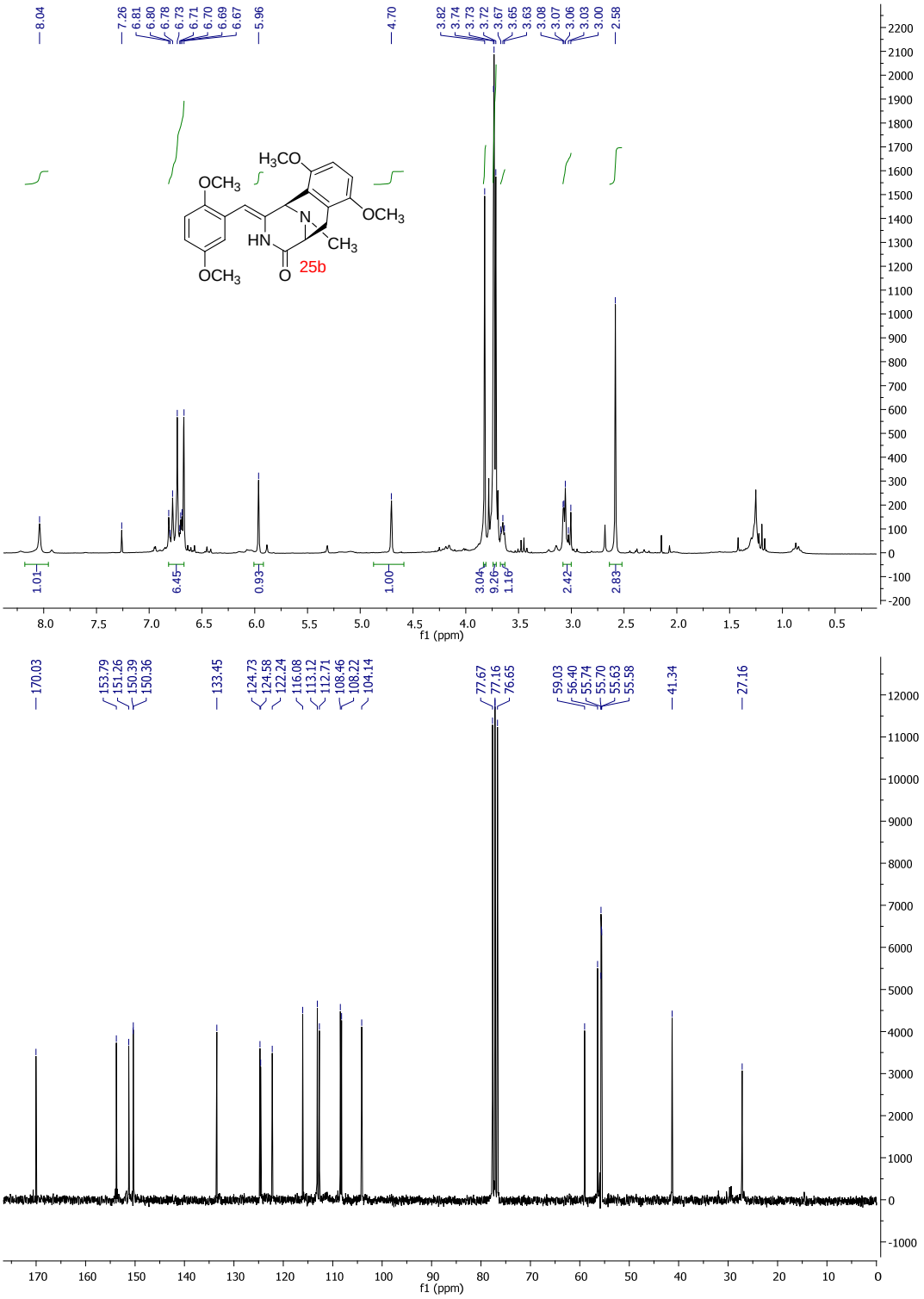
6.71
6.70
6.66
6.62
6.61
6.50
5.66
4.42
3.94
3.91
3.79
3.78
3.76
3.75
3.75
3.18
3.16
3.12
3.09
2.90
2.83
OCH3
OCH3
H3CO
H3CO
NH
HN
O
24b
0.99
1.09
0.84
1.22
1.33
1.15
1.18
1.01
1.30
12.61
1.02
2.21
f1 (ppm)


171.32
149.07
148.70
147.88
147.44
137.17
126.53
126.53
124.24
120.35
111.39
111.33
111.22
109.90
103.16
77.67
77.16
76.65
55.97
55.71
54.52
53.27
32.02
f1 (ppm)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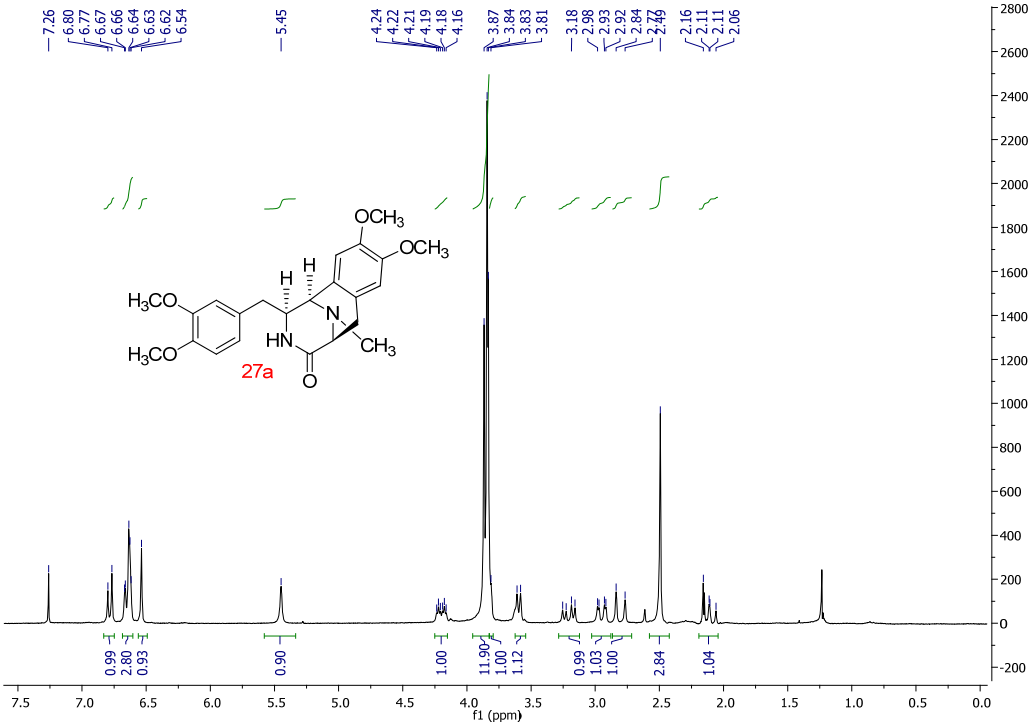
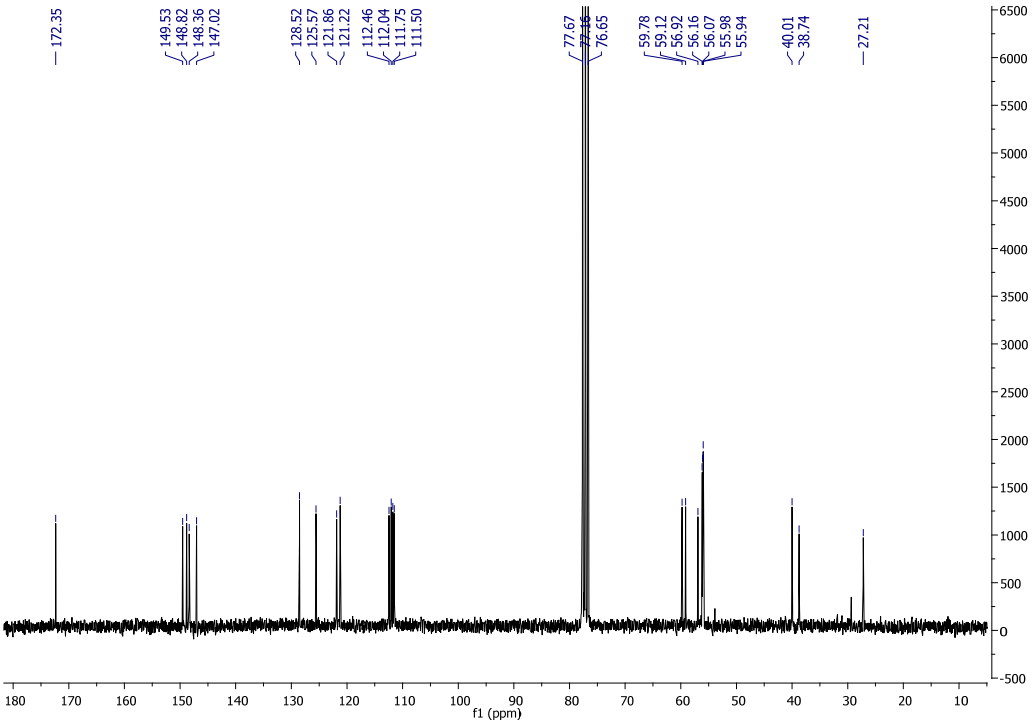
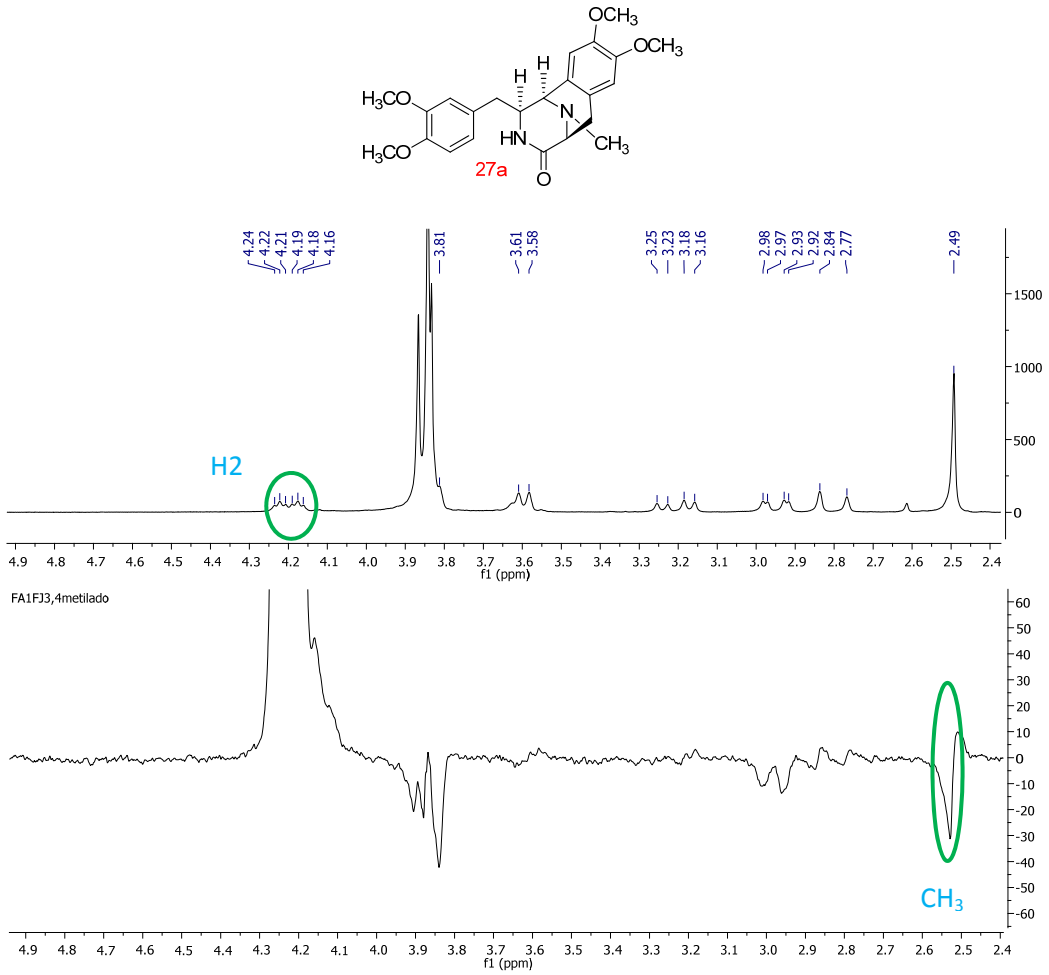
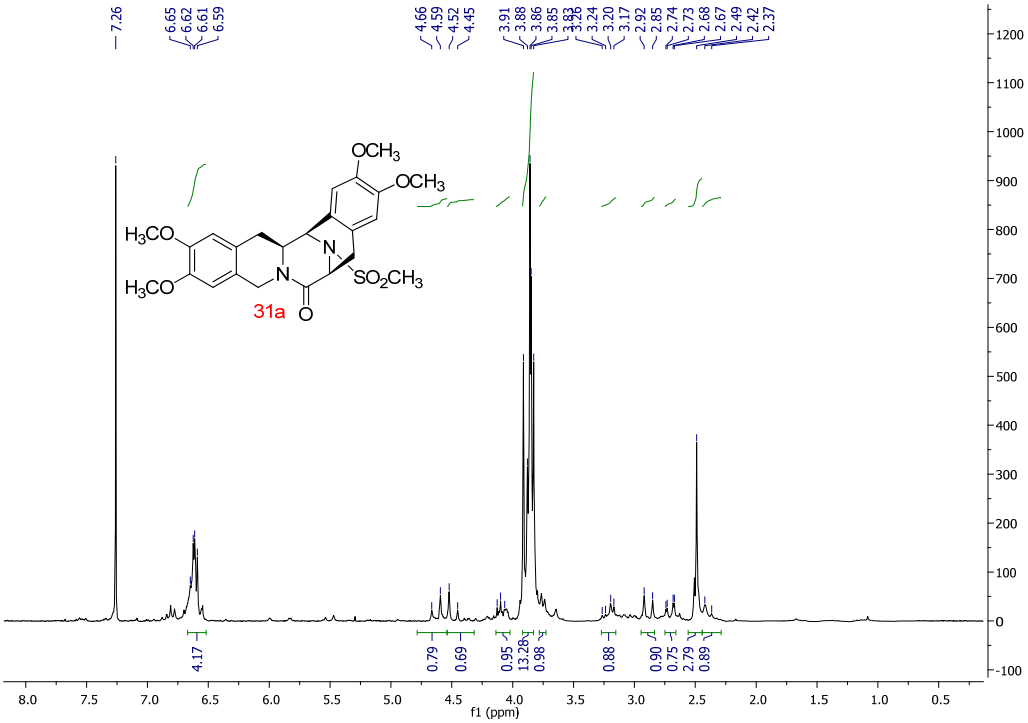
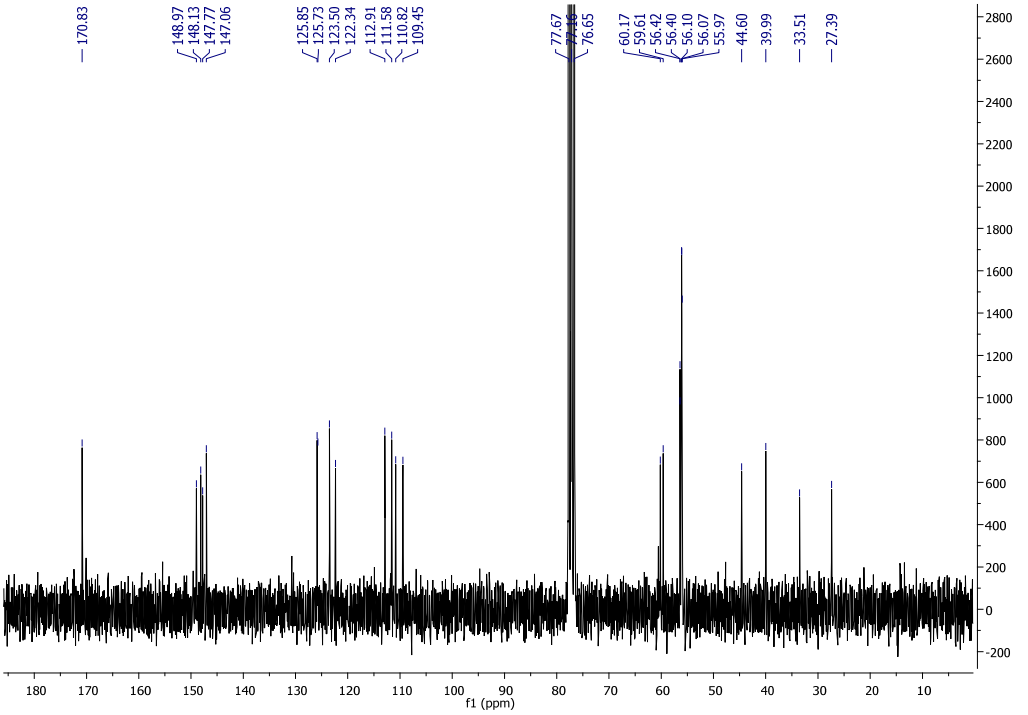
7.26
6.81
6.80
6.78
6.73
6.71
6.70
6.69
6.67
5.96
4.70
3.82
3.74
3.73
3.72
3.67
3.65
3.63
3.08
3.07
3.06
3.03
3.00
2.58
H3CO
OCH3
OCH3
OCH3
N
HN
CH3
O
25b
1.01
6.45
0.93
1.00
3.04
9.26
1.16
2.42
2.83
f1 (ppm)
170.03
153.79
151.26
150.39
150.36
133.45
124.73
124.58
122.24
116.08
113.12
112.71
108.46
108.22
104.14
77.67
77.16
76.65
59.03
56.40
55.74
55.70
55.63
55.58
41.34
27.16
f1 (ppm)

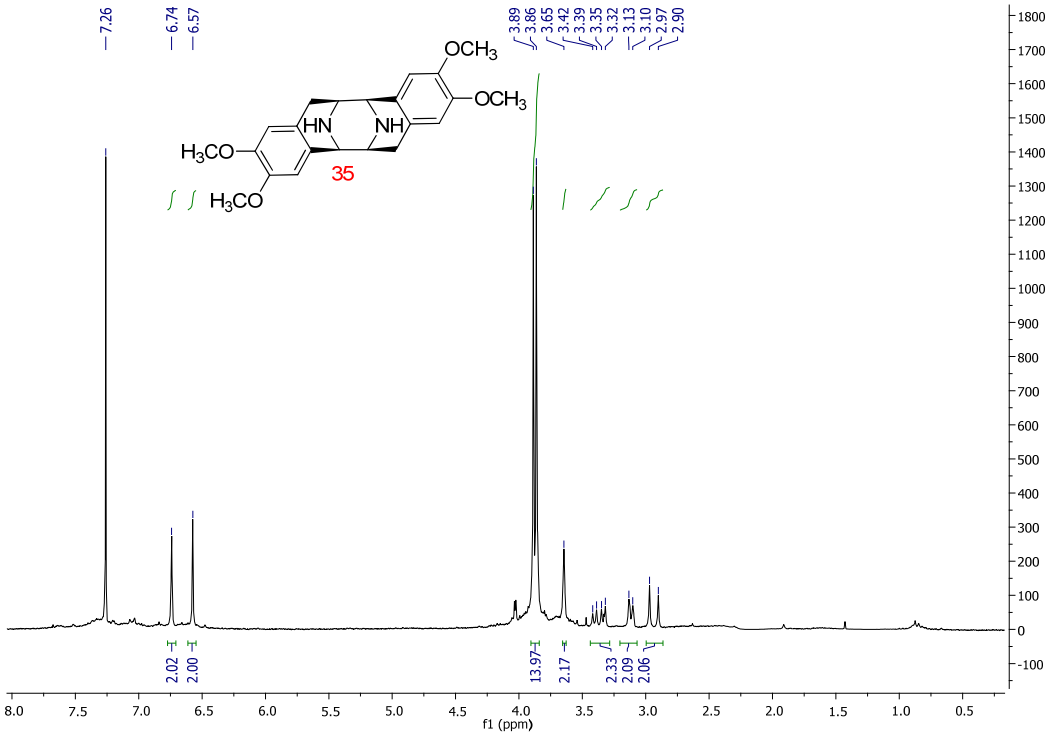

7.26
6.80
6.77
6.67
6.66
6.64
6.63
6.62
6.54
5.45
4.24
4.22
4.21
4.19
4.18
4.16
3.87
3.84
3.83
3.81
3.18
2.98
2.93
2.92
2.84
2.77
2.49
2.16
2.11
2.11
2.06
OCH3
OCH3
H
H
H3CO
N
HN
CH3
H3CO
O
27a
0.99
2.80
0.93
0.90
1.00
11.90
1.00
1.12
0.99
1.03
1.00
2.84
1.04
f1 (ppm)

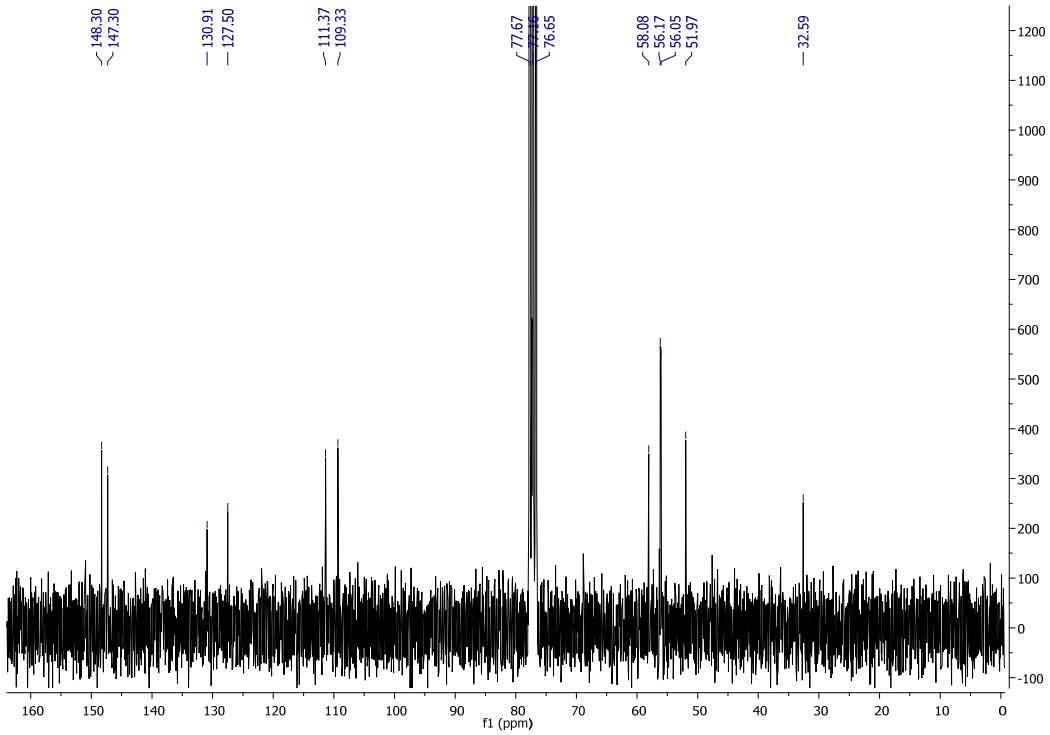

172.35
149.53
148.82
148.36
147.02
128.52
125.57
121.86
121.22
112.46
112.04
111.75
111.50
77.67
77.16
76.65
59.78
59.12
56.92
56.16
56.07
55.98
55.94
40.01
38.74
27.21
f1 (ppm)

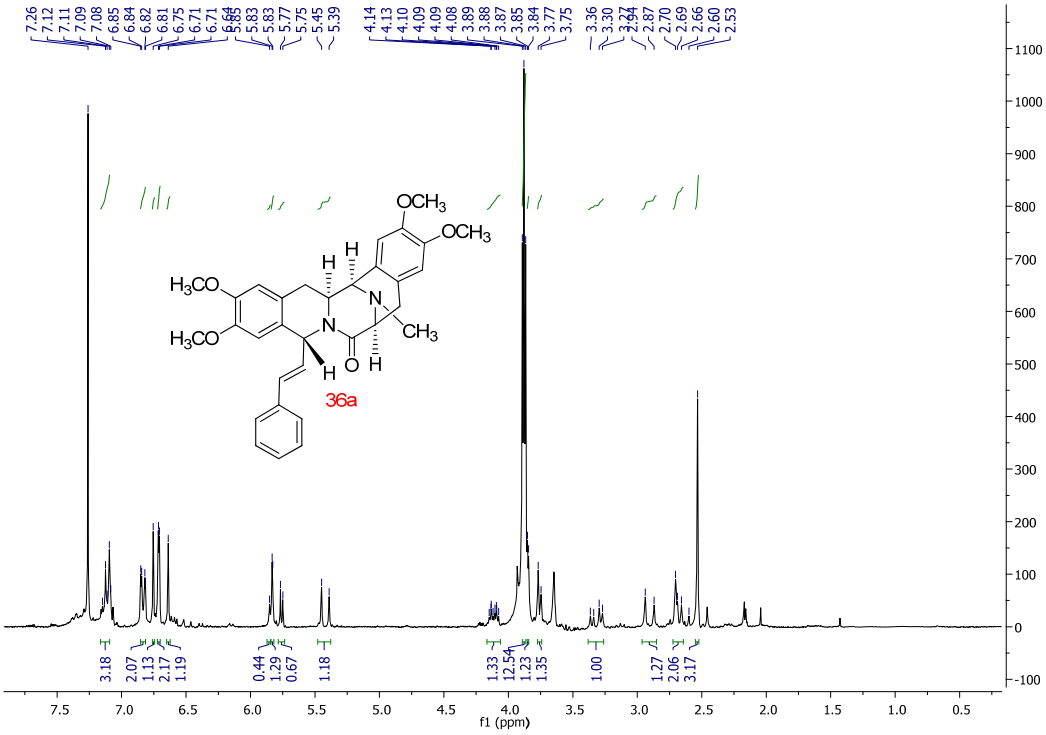

OCH3
OCH3
H
H
H3CO
H3CO
N
HN
CH3
O
27a
4.24
4.22
4.21
4.19
4.18
4.16
3.81
3.61
3.58
3.25
3.23
3.18
3.16
2.98
2.97
2.93
2.92
2.84
2.77
2.49
H2
f1 (ppm)
FA1FJ3,4metilado
CH3
f1 (ppm)

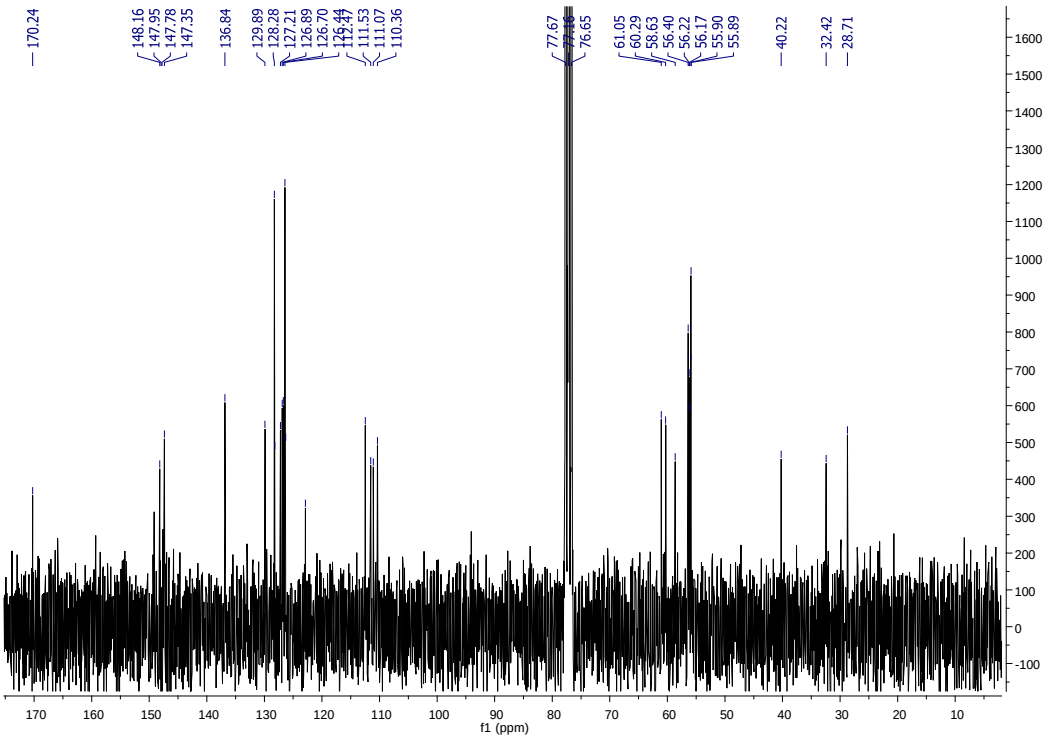

7.26
6.65
6.62
6.61
6.59
4.66
4.59
4.52
4.45
3.91
3.88
3.86
3.85
3.24
3.20
3.17
2.92
2.85
2.74
2.73
2.68
2.67
2.49
2.42
2.37
OCH3
OCH3
H3CO
H3CO
N
N
SO2CH3
O
31a
4.17
0.79
0.69
0.95
13.28
0.98
0.88
0.90
0.75
2.79
0.89
f1 (ppm)

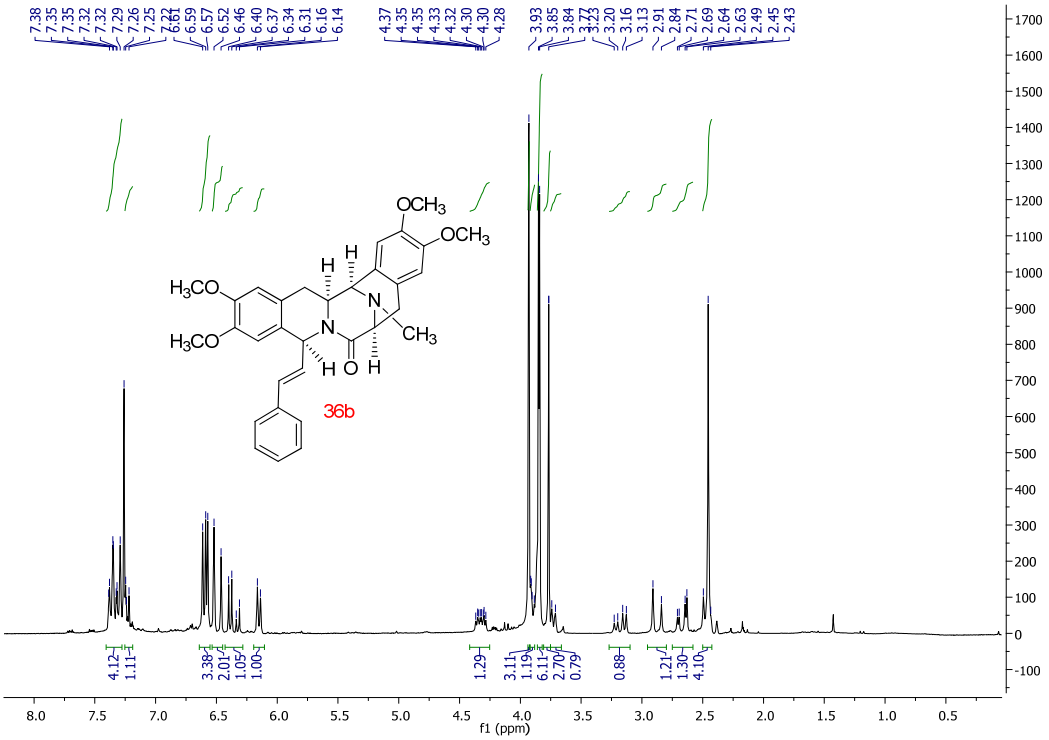

170.83
148.97
148.13
147.77
147.06
125.85
125.73
123.50
122.34
112.91
111.58
110.82
109.45
77.67
77.46
76.65
60.17
59.61
56.42
56.40
56.10
56.07
55.97
44.60
39.99
33.51
27.39
f1 (ppm)

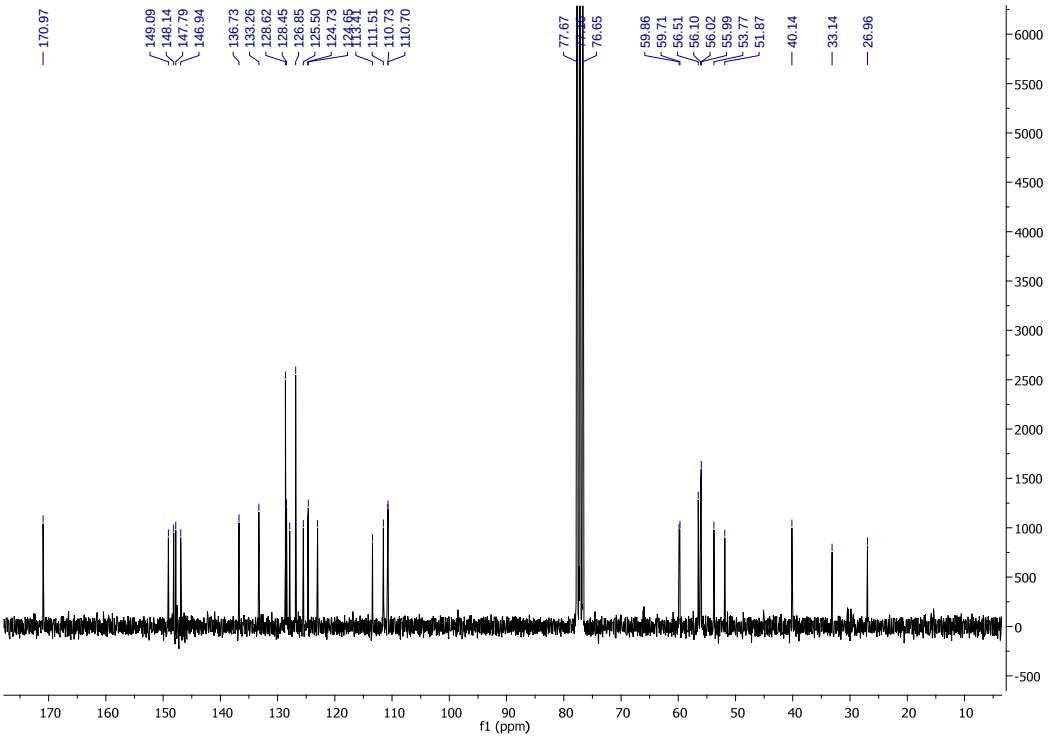

7.26
6.74
6.57
3.89
3.86
3.65
3.42
3.39
3.35
3.32
3.13
3.10
2.97
2.90
OCH3
OCH3
HN
NH
H3CO
H3CO
35
2.02
2.00
13.97
2.17
2.33
2.09
2.06
f1 (ppm)

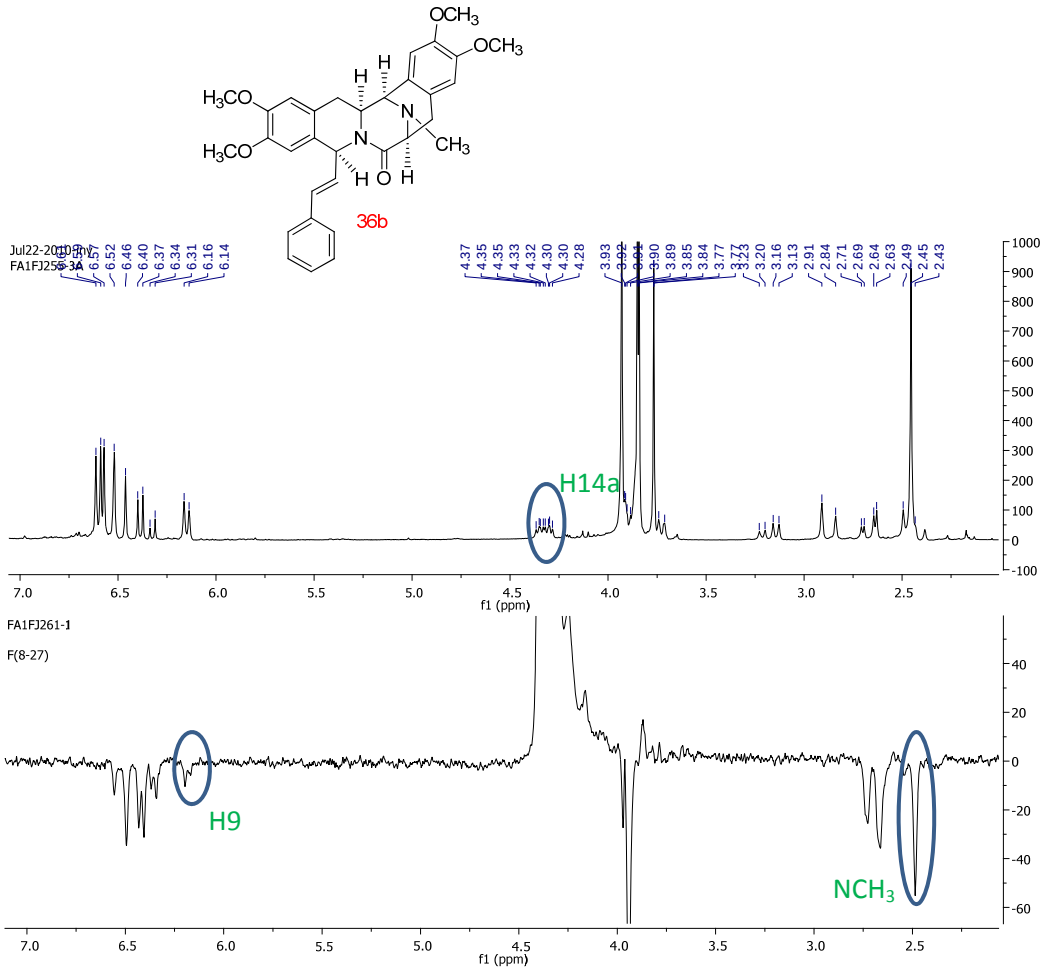

148.30
147.30
130.91
127.50
111.37
109.33
77.67
77.16
76.65
58.08
56.17
56.05
51.97
32.59
f1 (ppm)

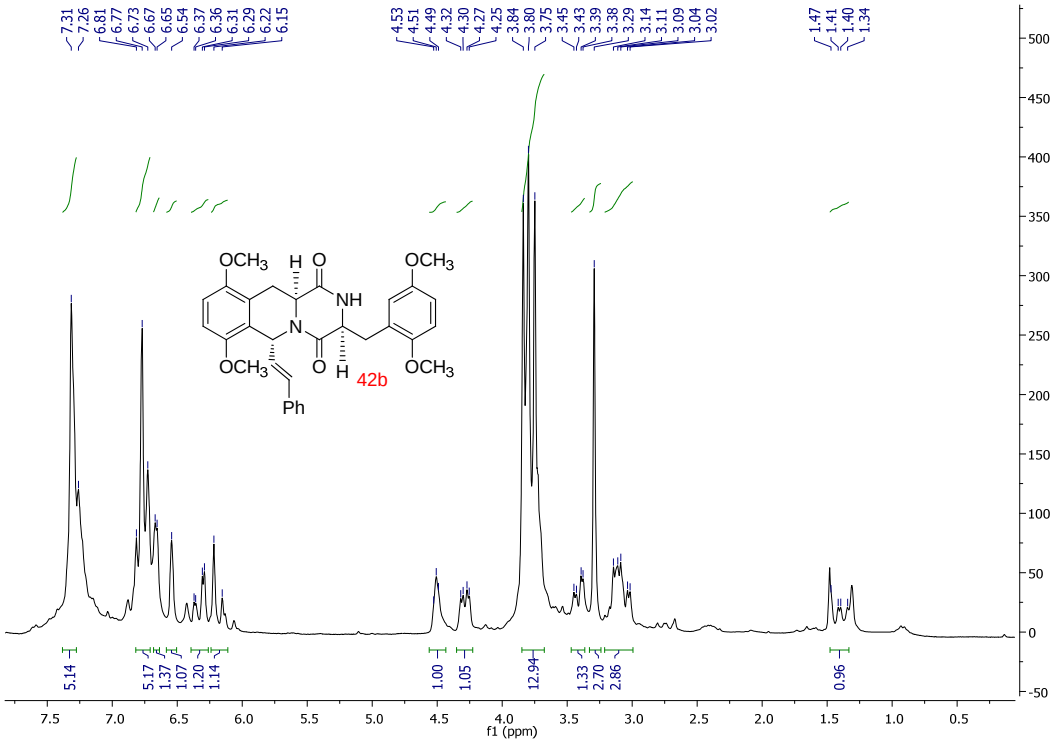

7.26
7.12
7.11
7.09
7.08
6.85
6.84
6.82
6.81
6.75
6.71
6.71
5.83
5.83
5.77
5.75
5.45
5.39
4.14
4.13
4.10
4.09
4.09
4.08
3.89
3.88
3.87
3.85
3.84
3.77
3.75
3.36
3.30
2.87
2.70
2.69
2.66
2.60
2.53
OCH3
OCH3
H3CO
H3CO
N
N
CH3
O
H
H
H
36a
3.18
2.07
1.13
2.17
1.19
0.44
1.29
0.67
1.18
1.33
12.54
1.23
1.35
1.00
1.27
2.06
3.17
f1 (ppm)

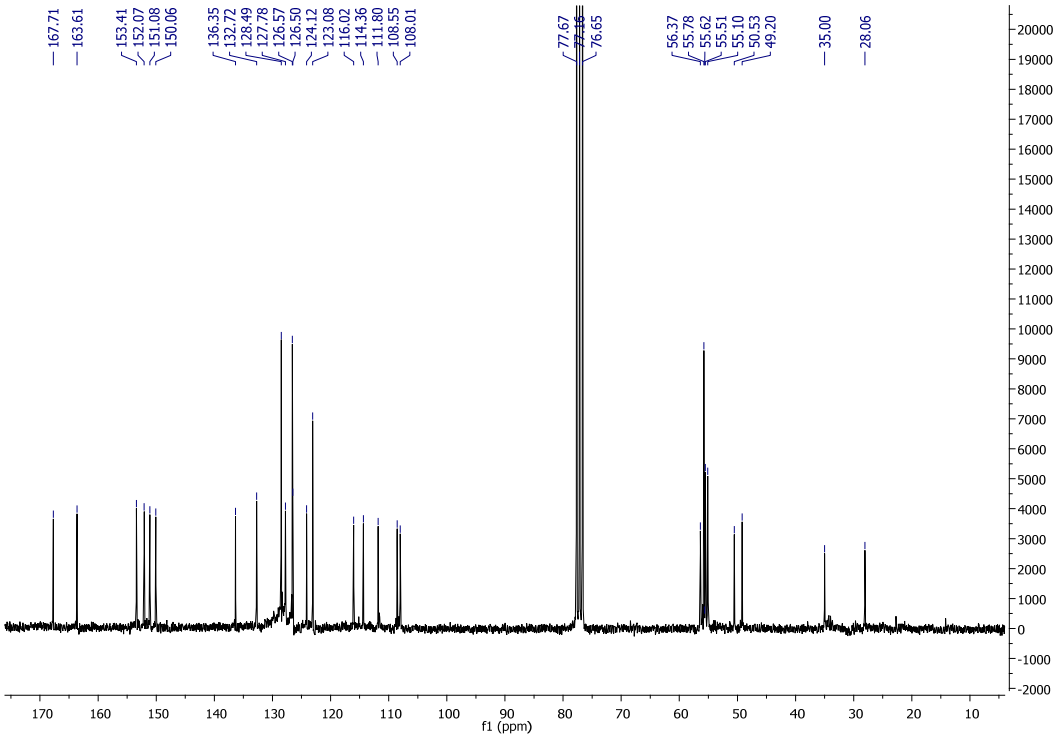

170.24
148.16
147.95
147.78
147.35
136.84
129.89
128.28
127.21
126.89
126.70
111.53
111.07
110.36
77.67
76.65
61.05
60.29
58.63
56.40
56.22
56.17
55.90
55.89
40.22
32.42
28.71
f1 (ppm)

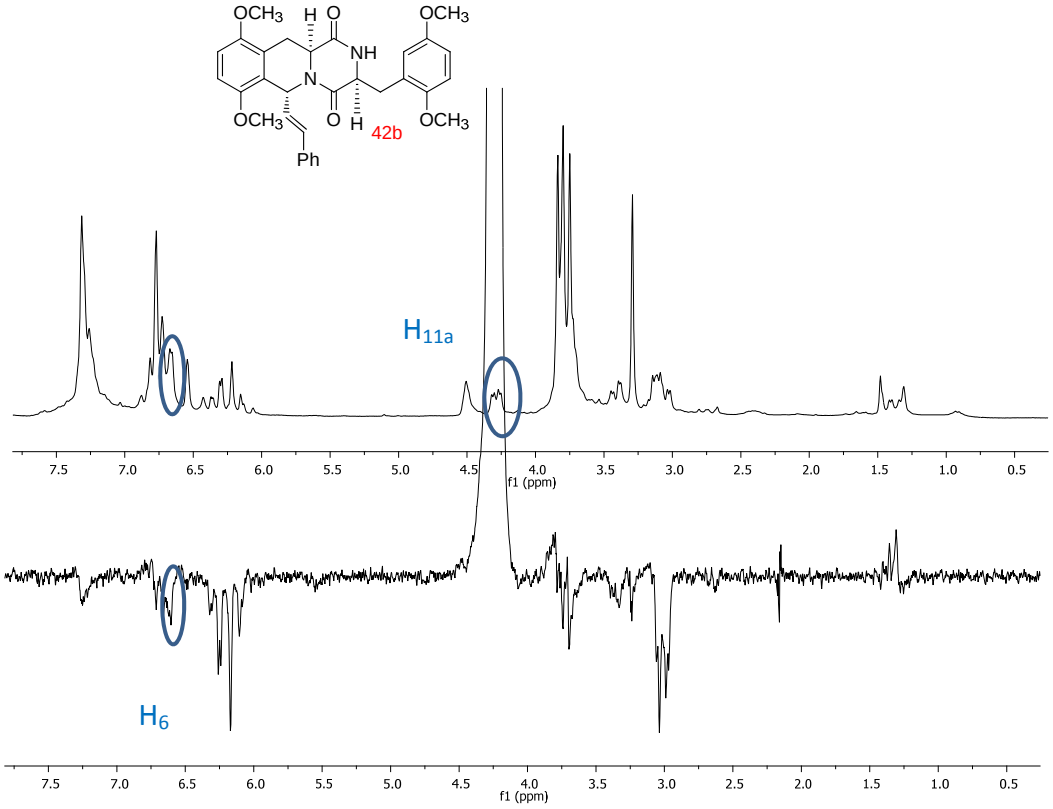

OCH3
OCH3
H3CO
H3CO
CH3
H
H
N
N
O
H
H
36b
f1 (ppm)

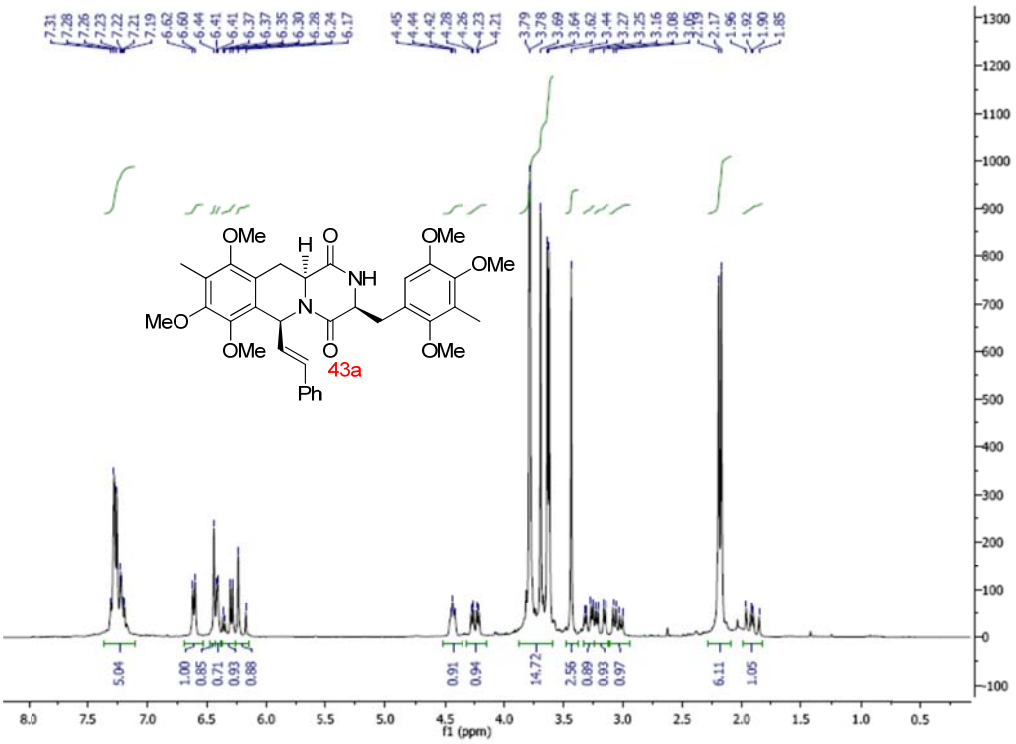

f1 (ppm)

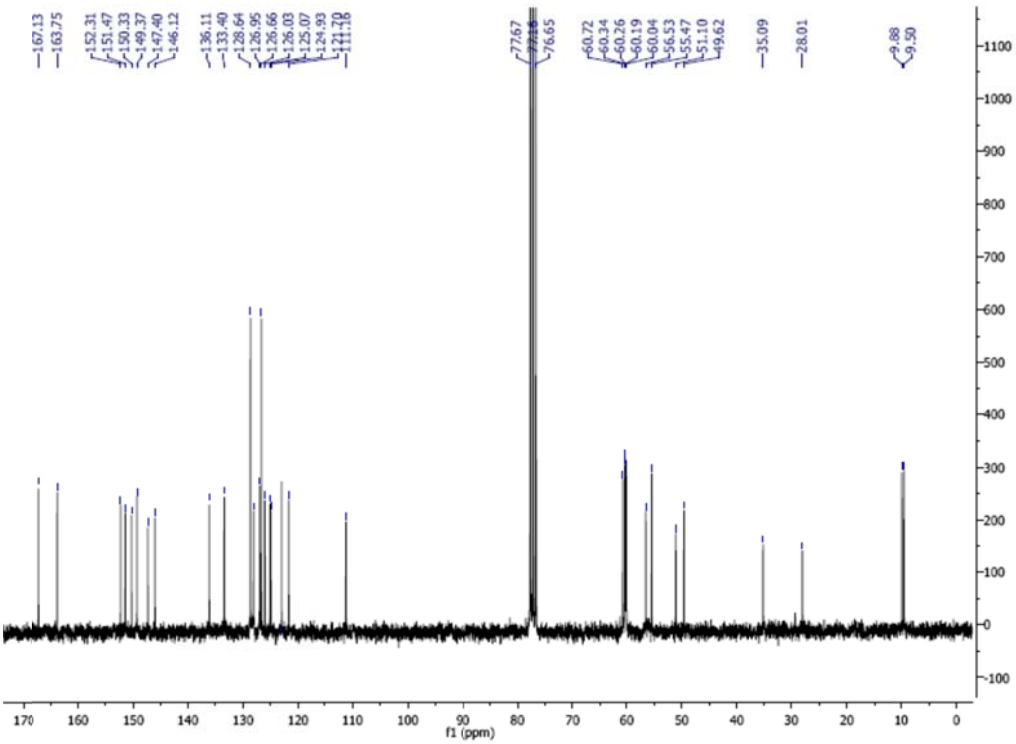

OCH3
OCH3
H3CO
H3CO
CH3
H O H
36b
H14a
H9
NCH3
f1 (ppm)

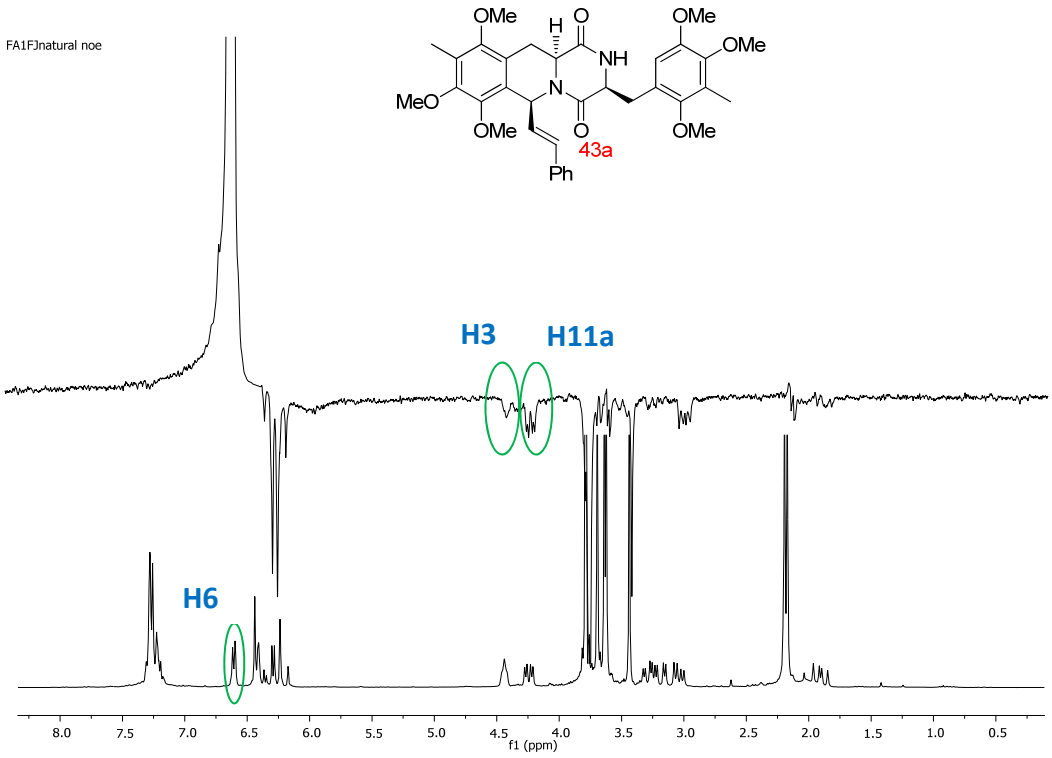

7.31
7.26
6.81
6.77
6.73
6.67
6.65
6.54
6.37
6.36
6.31
6.29
6.22
6.15
4.53
4.51
4.49
4.32
4.30
4.27
4.25
3.84
3.80
3.75
3.45
3.43
3.39
3.38
3.29
3.14
3.11
3.09
3.04
3.02
1.47
1.41
1.40
1.34
OCH3
H
O
NH
N
O
H
OCH3
OCH3
OCH3
Ph
42b
5.14
5.17
1.37
1.07
1.20
1.14
1.00
1.05
12.94
1.33
2.70
2.86
0.96
f1 (ppm)

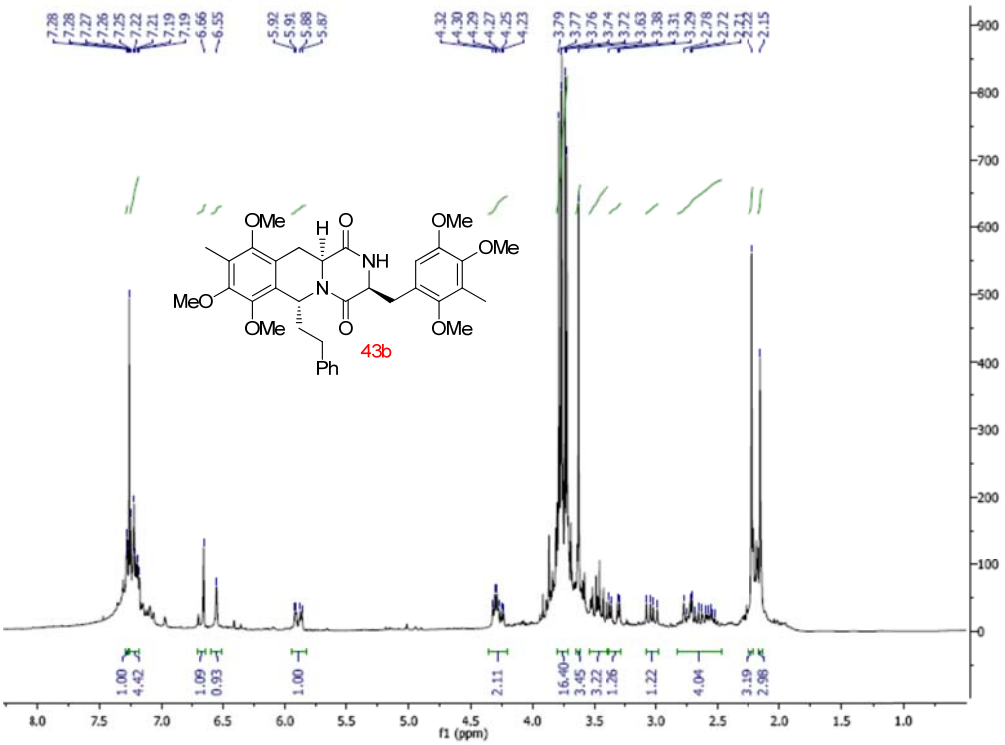

167.71
163.61
153.41
152.07
151.08
150.06
136.35
132.72
128.49
127.78
126.57
126.50
124.12
123.08
116.02
114.36
111.80
108.55
108.01
77.67
77.16
76.65
56.37
55.78
55.62
55.51
55.10
50.53
49.20
35.00
28.06
f1 (ppm)

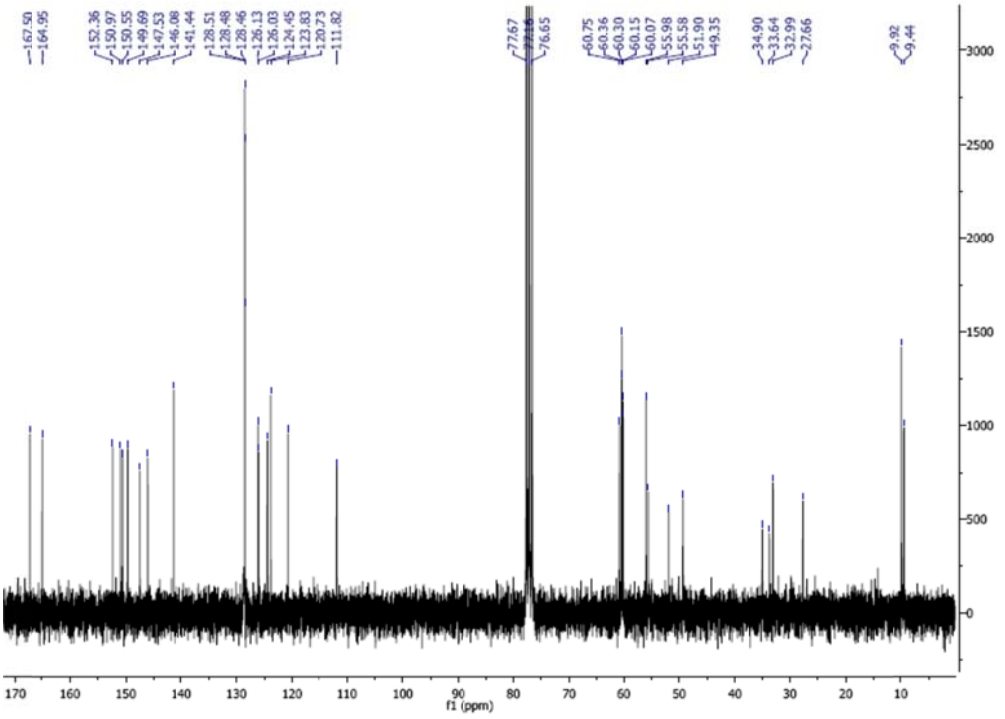

OCH3
H
O
OCH3
NH
N
OCH3
O
H
OCH3
Ph
42b
H11a
H6
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

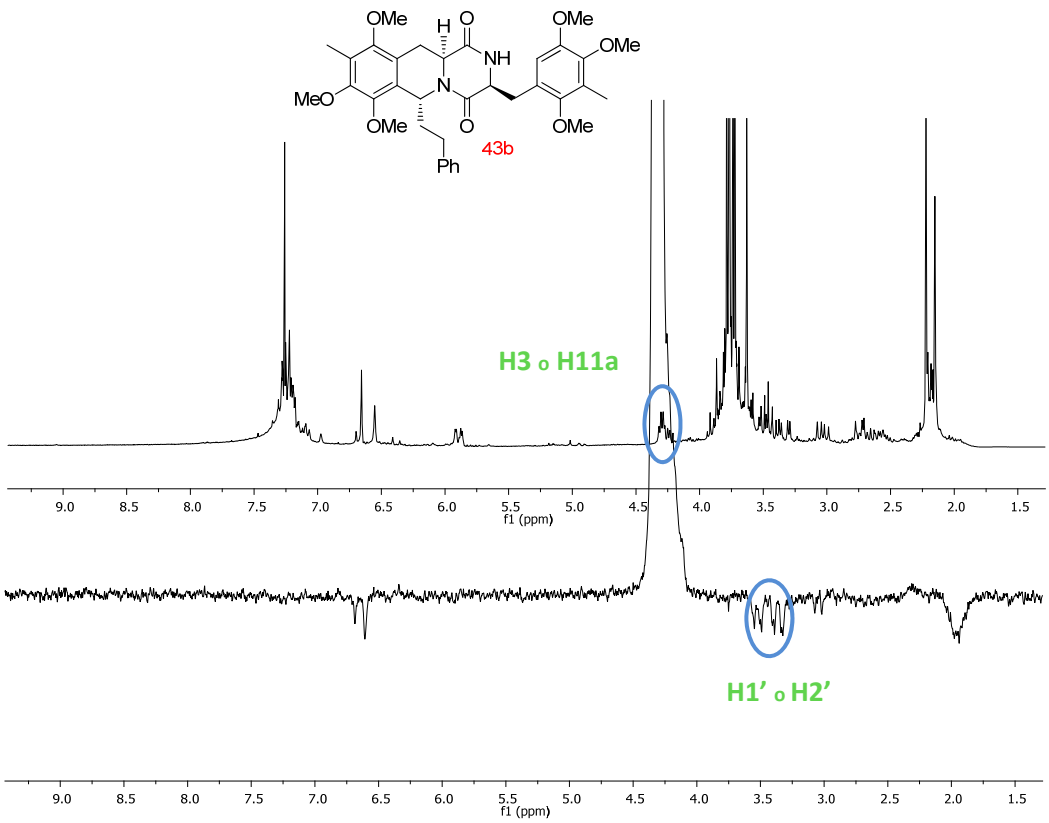

OMe
H
O
NH
OMe
OMe
MeO
N
OMe
O
OMe
43a
Ph
f1 (ppm)

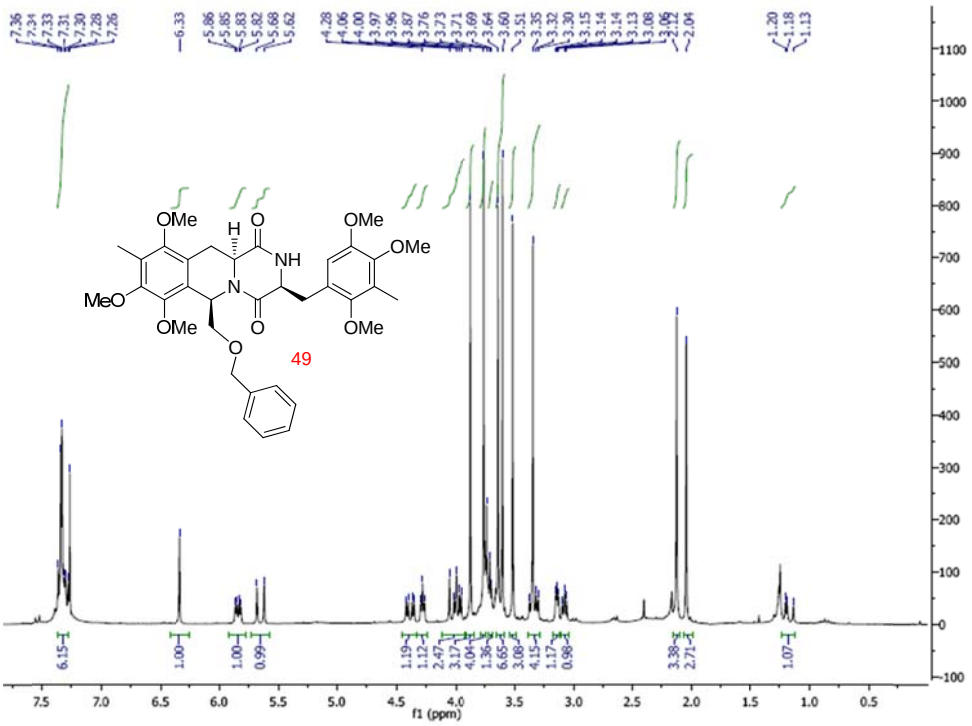

f1 (ppm)

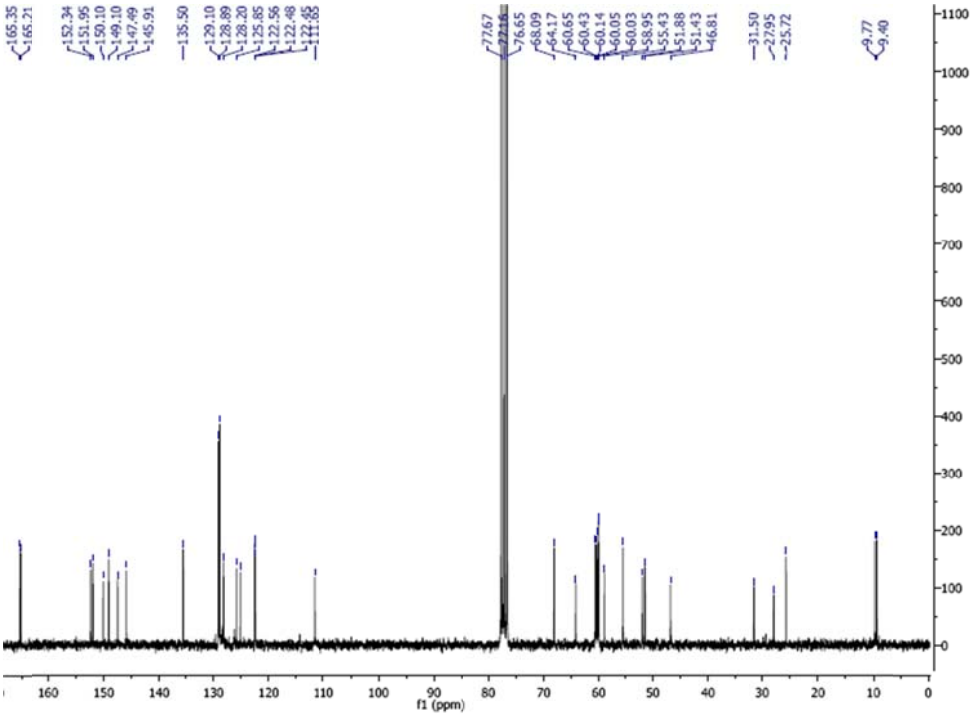

FA1FJnatural noe
OMe
H
O
OMe
NH
OMe
MeO
N
OMe
O
OMe
43a
Ph
H3
H11a
H6
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

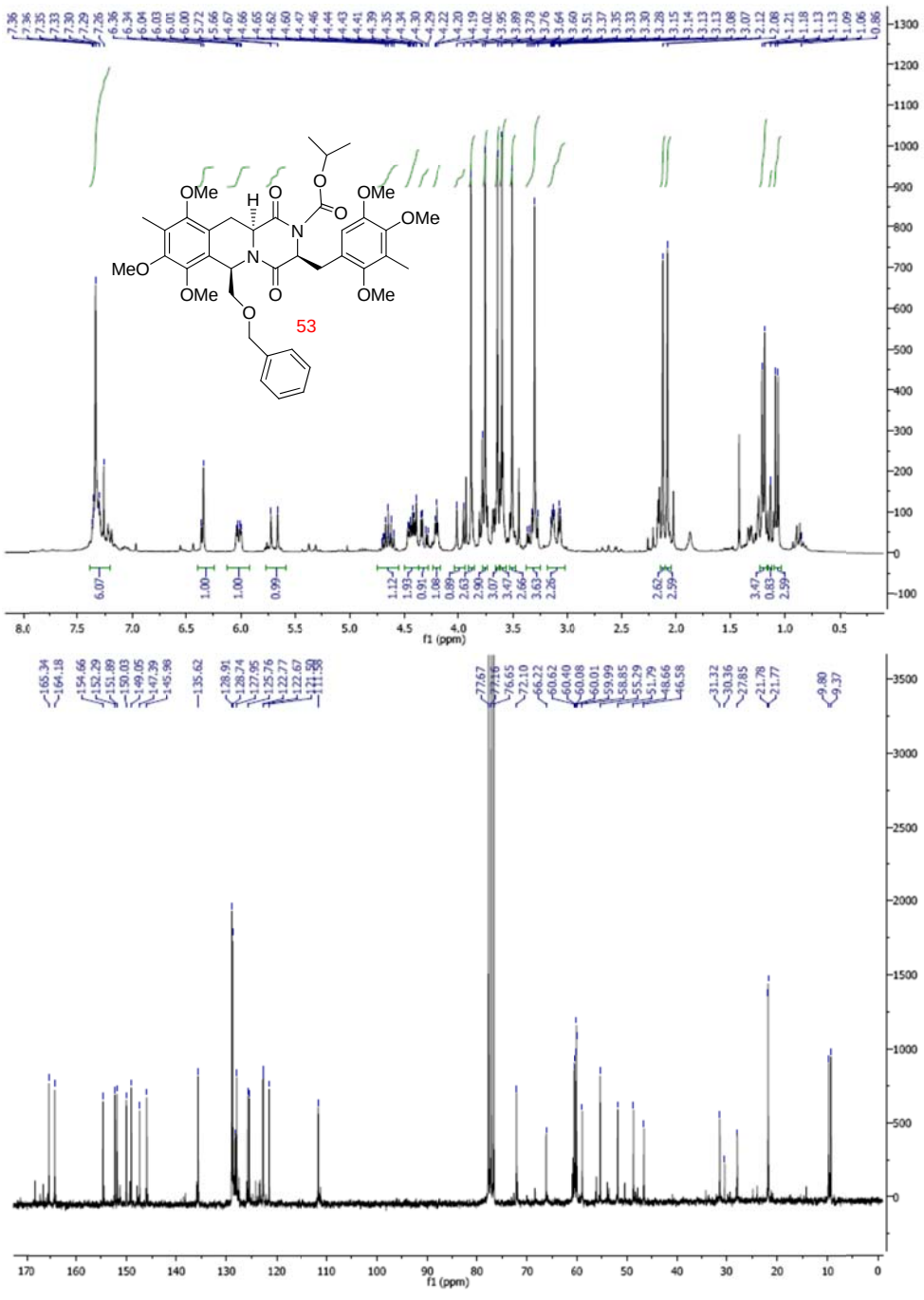

OMe
H
O
OMe
OMe
NH
MeO
N
OMe
O
OMe
Ph
43b
f1 (ppm)

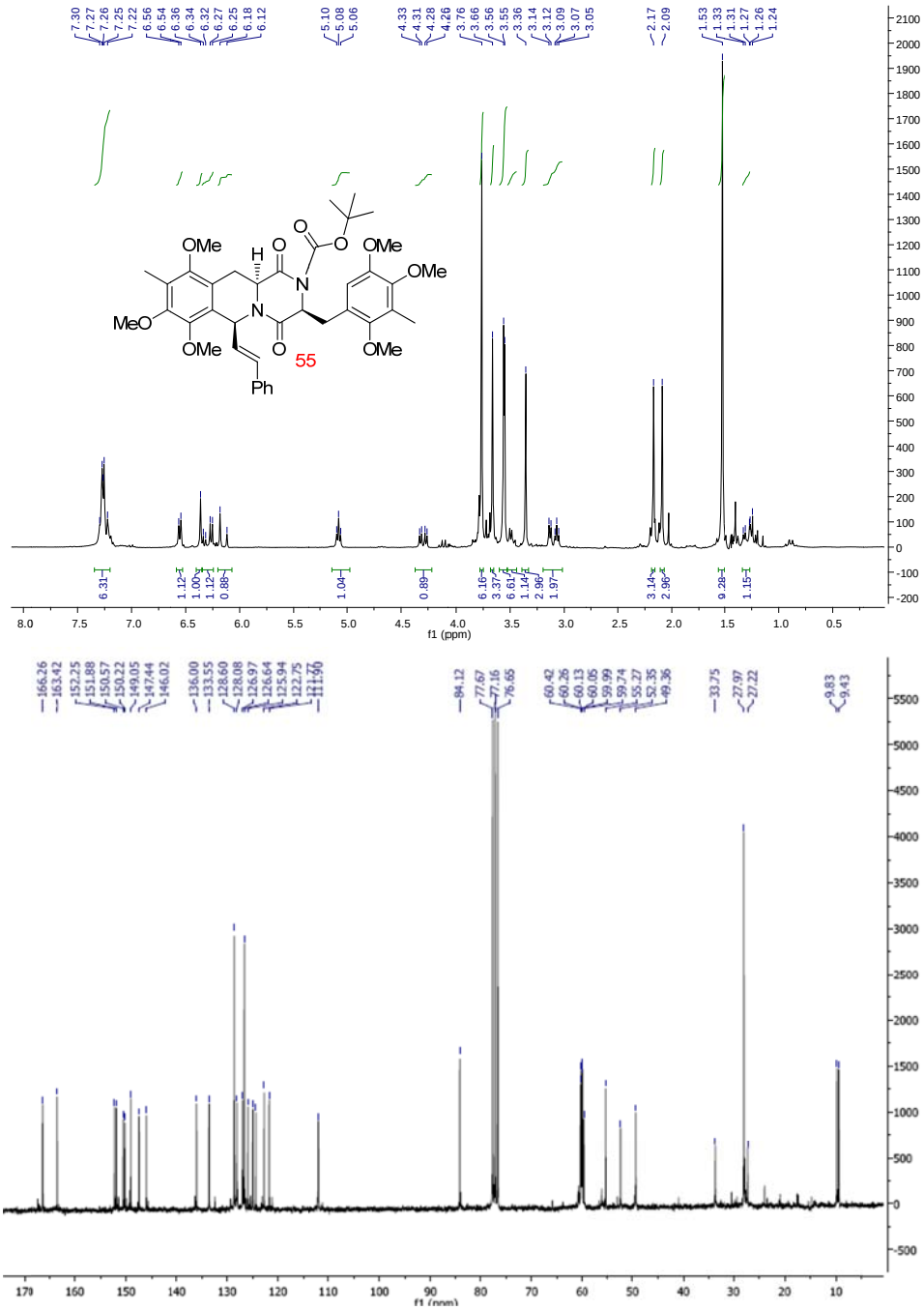

f1 (ppm)


OMe
H
O
OMe
OMe
NH
MeO
N
OMe
O
OMe
Ph
43b
H3 o H11a
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)
H1' o H2'


OMe
H
O
NH
OMe
OMe
MeO
N
OMe
O
OMe
O
49
f1 (ppm)


f1 (ppm)


OMe
H
O
O
OMe
OMe
N
MeO
N
OMe
O
OMe
O
O
53
f1 (ppm)
f1 (ppm)


7.30
7.27
7.26
7.25
7.22
6.56
6.54
6.36
6.34
6.32
6.27
6.25
6.18
6.12
5.10
5.08
5.06
4.33
4.31
4.28
4.26
3.76
3.66
3.56
3.55
3.36
3.14
3.12
3.09
3.07
3.05
2.17
2.09
1.53
1.33
1.31
1.27
1.26
1.24
OMe
MeO
OMe
OMe
OMe
OMe
H
N
N
O
O
O
O
Ph
55
f1 (ppm)
166.26
163.42
152.25
151.88
150.57
150.22
149.05
147.44
146.02
136.00
133.55
128.60
128.08
126.97
126.64
125.94
122.75
94.12
77.67
77.16
76.65
60.42
60.26
60.13
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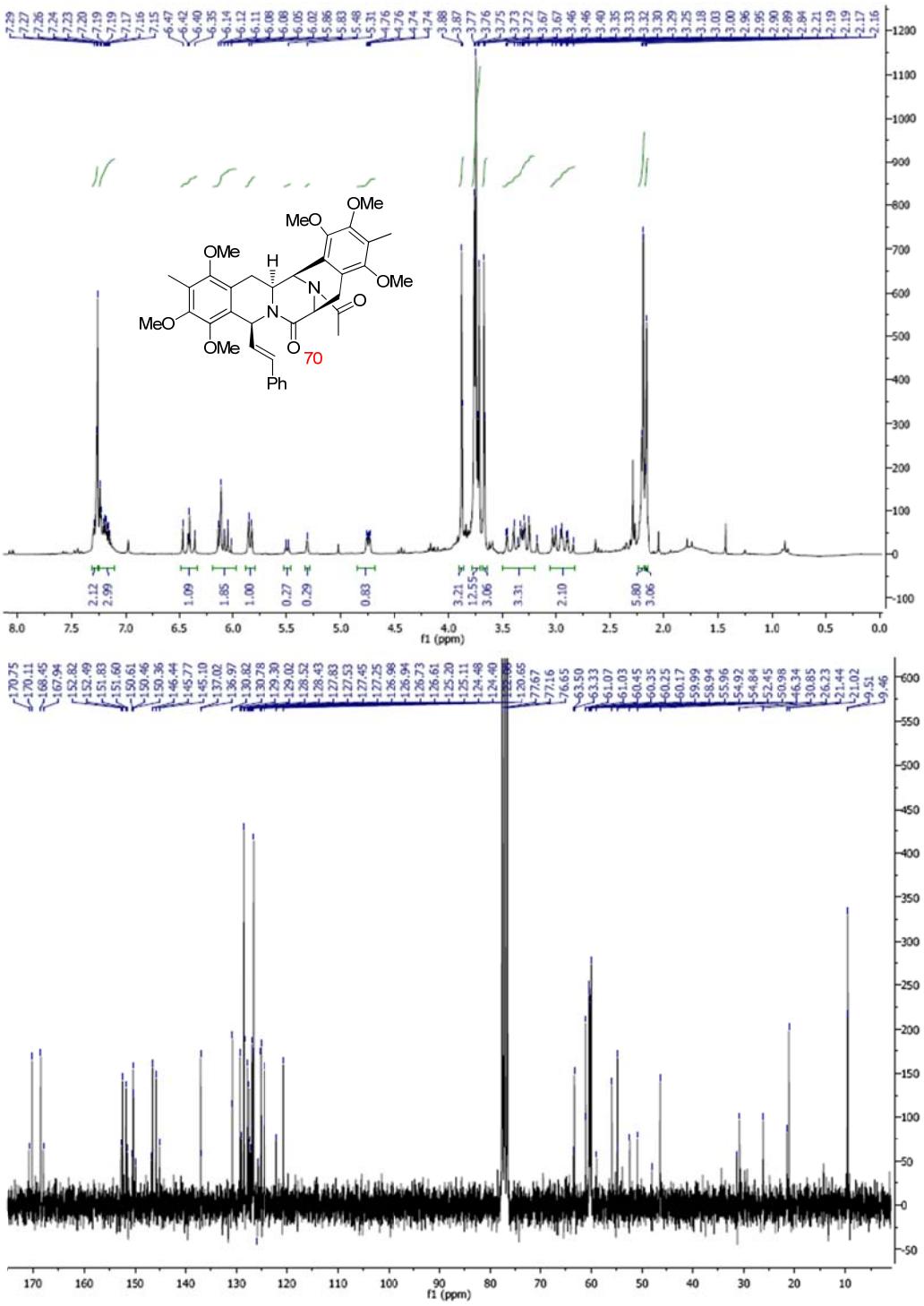
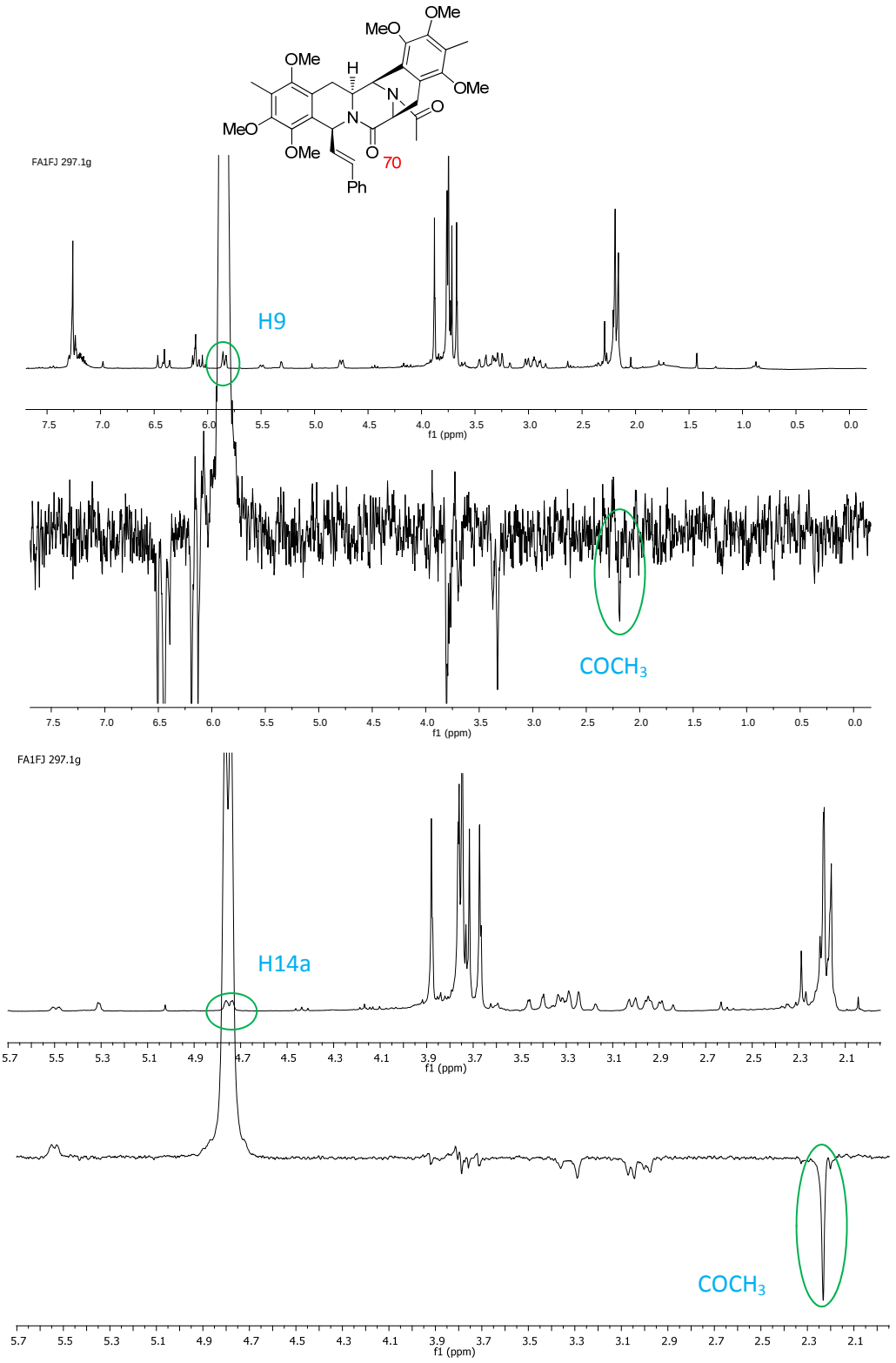
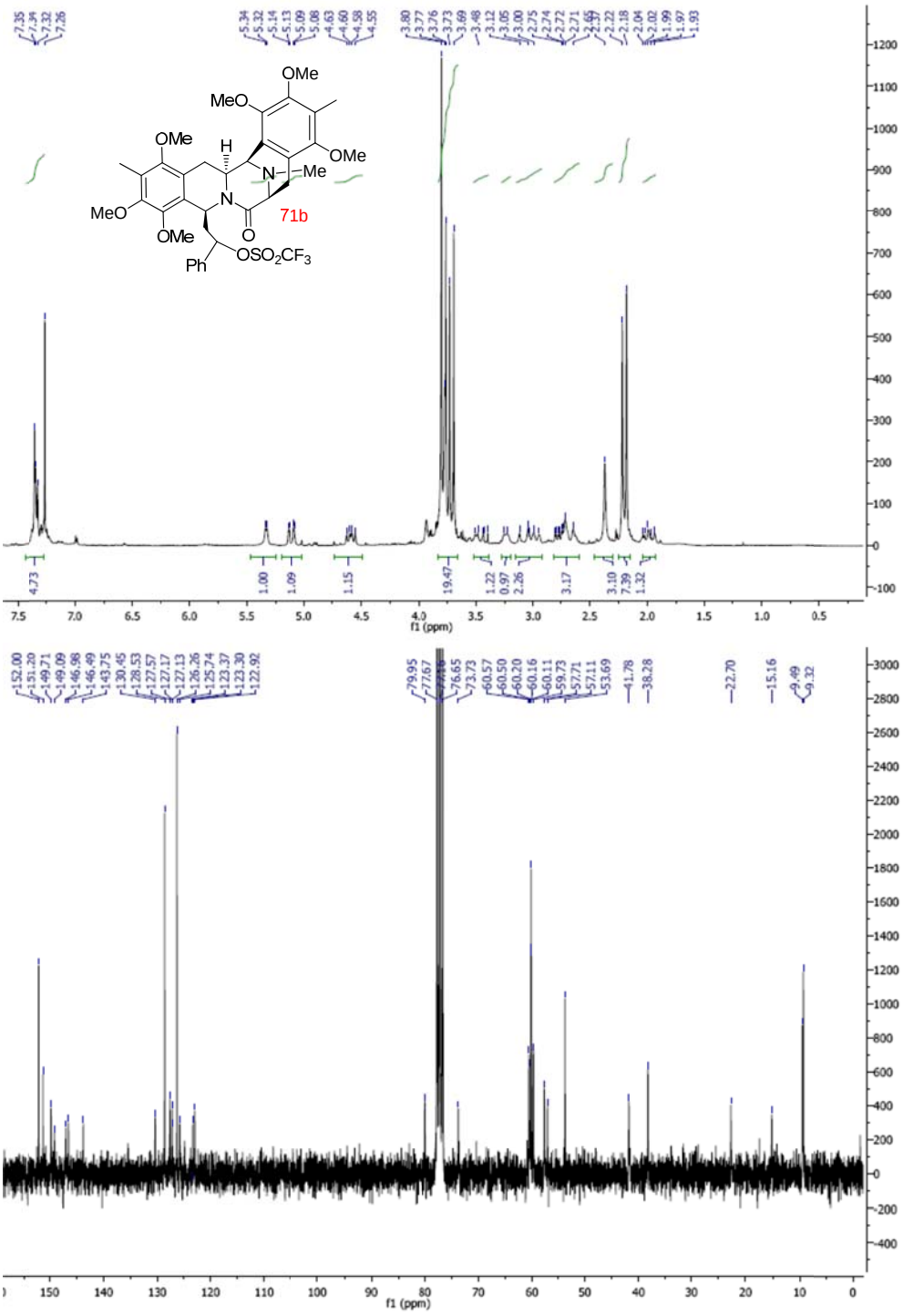
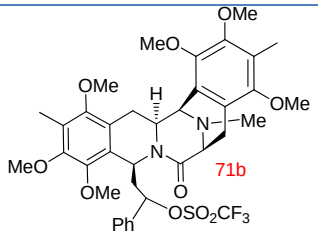
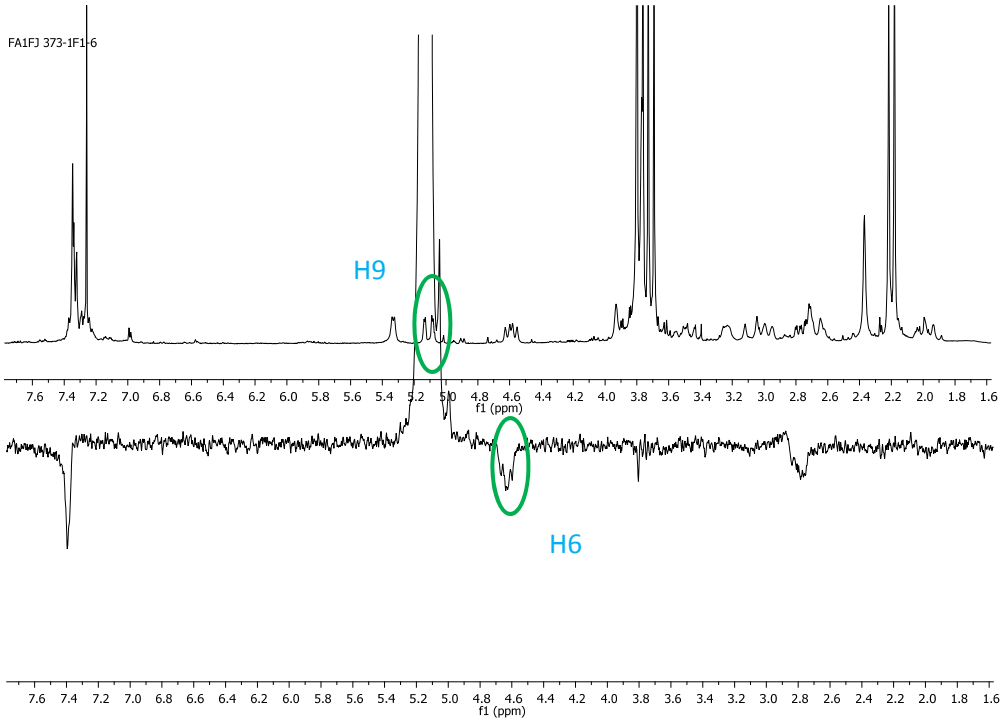
33.75
27.97
27.22
9.83
9.43
f1 (ppm)


OMe
MeO
OMe
H
N
OMe
MeO
N
O
O
OMe
O
70
Ph
f1 (ppm)
f1 (ppm)


OMe
MeO
OMe
H
N
OMe
MeO
N
O
OMe
O
70
Ph
FA1FJ 297.1g
H9
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
COCH3
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
FA1FJ 297.1g
H14a
5.7 5.5 5.3 5.1 4.9 4.7 4.5 4.3 4.1 3.9 3.7 3.5 3.3 3.1 2.9 2.7 2.5 2.3 2.1
f1 (ppm)
COCH3
5.7 5.5 5.3 5.1 4.9 4.7 4.5 4.3 4.1 3.9 3.7 3.5 3.3 3.1 2.9 2.7 2.5 2.3 2.1
f1 (ppm)


OMe
MeO
OMe
H
N
Me
OMe
MeO
N
71b
OMe
O
Ph
OSO2CF3
f1 (ppm)


OMe
MeO
OMe
H
OMe
N
Me
N
MeO
71b
OMe
O
Ph
OSO2CF3


FA1FJ 373-1F1-6
H9
H6
f1 (ppm)